Study Details	Patients/Interventions	Methods	Outcomes/Results
High participation, low attrition, multivariate analysis controlled for most potential confounders, cardiac events mostly comprised of QTc prolongation ≥500 ms which is a surrogate outcome for serious cardiac risk.	6 months before their first methadone purchase in 2010 (study index date). **Exclusion Criteria:** The study excluded patients if they were on methadone for addiction because they procured their methadone outside of the KPCO pharmacy system.	chronic methadone use status, concomitant uses of QT-prolonging and CYP3A4-inhibiting medications, diagnosis of CHF, methadone dose at index date, dose ≥100 mg at any time during follow-up, and days of methadone supply during follow-up. **Follow-up:** 12 months	
Reference: Turner et al. 2014[5] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To identify primary care COT patient and opioid regimen characteristics associated with aberrant UDT results. **Quality Rating:** Fair High participation from large primary care population, low attrition, multivariable analysis controlled for most (but not all) relevant potential confounders. Since most patients were on low-moderate doses of short-acting opioids, findings may not be generalizable to other settings with a higher proportion of substance abuse and higher dose opioid prescriptions.	**Number of Patients:** 3809 patients with 5420 UDTs **Diagnosis:** CNCP **Age (Years):** ≥20 years, mean and range not reported **Gender:** 60.6% female **Inclusion Criteria:** all pain management UDTs performed January 2011–December 2012 for patients aged ≥20 years. UDT, pharmacy, and patient data was obtained from GH databases. The authors included only UDTs for patients on COT, defined by GH as ≥70 days' opioid supply in the prior 90 days. **Exclusion Criteria:** To limit the sample to UDTs for CNCP patients, we excluded those of patients who, in the one-year period prior to the UDT, had had hospice care, opioid prescriptions from oncologists, or more than one visit for cancer other than non-melanoma skin cancer. To ensure data availability, we excluded UDTs for patients not continuously enrolled at GH for the previous year.	The pain management UDT includes a screening immunoassay and liquid chromatography-tandem mass spectrometry confirmatory test. The authors conducted descriptive analyses, then logistic regression analyses predicting dilute samples and the following UDT results (excluding dilute samples): (1) any aberrancy; (2) prescribed opioid non-detection (defined as negative for all opioids prescribed for prior 90 days); (3) THC but no illicit drug; (4) non-prescribed opioid; (5) illicit drug; and (6) non-prescribed benzodiazepine. Potential predictors included age, gender race, ethnicity, mental health diagnosis, alcohol used disorder, substance use disorder, current smoker, opioid daily MED, days supply, and opioid type (short or long-acting). All predictors were entered in a multivariable model for each outcome that had sufficient counts for reliable results. **Follow-up:** Patient visit diagnoses were identified within 2 years prior to the index UDT.	**Any Aberrant Result**: In multivariable analyses, adjusted odds ratios (AOR) and 95% CI: for any aberrant result were higher for 1) males (OR 1.24 [1.07–1.43]), 2) patients with prior SUD diagnoses (OR 1.42 [1.17–1.72]), and 3) current smokers versus non-smokers (OR 1.50 [1.30–1.73]). They were lower for: 1) patients aged 45–64 (OR 0.77 [0.65, 0.92]) and 65+ (OR 0.40 [0.32, 0.50]) vs patients aged 20–44, 2) those on 40–<120 mg daily MED (OR 0.78 [0.65, 0.95]) versus <40 mg MED, and 3) for patients on long-acting opioids only (OR 0.72 [0.55, 0.95]) or long-acting plus short-acting opioids (OR 0.67 [0.54, 0.83]) vs short-acting opioids only. **Prescribed Opioid Non-detection** was more likely among patients with prior SUD diagnoses (OR 1.70; 95 % CI 1.31, 2.20). It was less likely among: 1) patients aged 45+ versus 20–44, 2) on moderate (OR 0.52 [0.39, 0.70]) or high (OR 0.22 [0.11, 0.43]) doses vs low doses, 3) with daily/near-daily opioid supply versus less-than-daily supply (0.78 [0.63, 0.96]), and 4) on long-acting opioids (versus short-acting opioids only).

Study Details	Patients/Interventions	Methods	Outcomes/Results
			Non-prescribed Opioids were more common among: 1) African-Americans than whites (OR 2.07 [1.16, 3.69]) and 2) among patients with excessive (versus less than-daily) opioid supply (1.59 [1.03, 2.46]), and less common among patients aged 45+ versus 20–44.
Reference: Zedler et al. 2014[13] **Country:** USA **Study Design:** Retrospective nested case-control study **Purpose:** To examine factors associated with a diagnosis of serious opioid-related respiratory/CNS depression or overdose among VHA patients who were dispensed an opioid by VHA. **Quality Rating:** Poor Study did not report percent patients with acute or chronic pain or percent of patients with short-term opioid therapy vs. COT.	**Number of Patients:** 8,987 veterans **Diagnosis:** Pain diagnoses were not reported **Age (Years):** Median 62 years **Gender:** 92.1% male **Inclusion Criteria:** The study used VHA Medical SAS datasets from October 1, 2010 through September 30, 2012. "Cases" were defined as 1) patients who were dispensed at least one opioid prescription by VHA, identified by national drug code; and 2) had a claim for a serious opioid-related toxicity or overdose event based on ICD-9-CM codes and CPT codes. All patients were required to have non-missing age, sex, and race values in addition to continuous medical and pharmacy benefits in the 6 months before the index date (the "baseline period"). For each case, 10 control patients were randomly selected and assigned from those who 1) were dispensed an opioid by VHA during the study period; 2) did not experience serious opioid-related toxicity or overdose as defined in the study; and 3) had complete data for age, sex, and race. **Exclusion Criteria:** Not reported	The study included 817 cases and 8,170 controls. A serious opioid-related toxicity or overdose event was defined as follows: 1) a listed CNS or respiratory adverse effect code in addition to a listed poisoning event or external cause code occurring within ±1 day of the adverse effect; or 2) use of mechanical ventilation or critical care in addition to a listed poisoning event or external cause code occurring within ±1 day of the critical respiratory support. The first identified occurrence of opioid-related overdose or life-threatening respiratory/CNS depression ("index event") during the study period served as the "index date" for cases. Multivariable analysis was performed using conditional logistic regression to examine factors potentially associated with the index event of serious opioid-related toxicity or overdose. The covariates included in the regression model were age, sex, race/ethnicity, marital status, US Census region, comorbidities, prescription opioid characteristics, the maximum prescribed daily MED, selected non-care resource utilization. opioid prescription medications, and baseline health **Follow-up:** Baseline period covered 6 months prior to the index event. For cases, the follow-up period was calculated as the number of days after the end of the event until death, disenrollment, or the end of the study period.	**Risk Factors for Serious Opioid-related Respiratory/CNS Depression or Overdose.** The multivariable analysis identified the following variables as having the strongest associations with the outcome: 1) History of opioid dependence (OR 3.9, 95% CI: 2.6-5.8), 2) Max prescribed daily opioid MED ≥100 mg/day (OR 4.1, 95% CI: 2.6-6.5), 3) ≥1 day of hospitalization during prior 6 months (OR 2.9, 95% CI: 2.3-3.6) Other factors that showed smaller significant associations (and smaller ORs) with the outcome were: 1) Age groups 45–54 and 55–64 years (vs.18–34 years), 2) Race (non-Hispanic white vs. non-Hispanic black, 3) Marital status widowed or never married, 4) Geographic region West, 5) COPD, 6) Use of warfarin, 7) Renal disease, 8) Skin ulcers, 9) Moderate or severe liver disease, 10) Metastatic solid tumor, 11) Substance abuse and nonopioid substance dependence 12) Pancreatitis,

Study Details	Patients/Interventions	Methods	Outcomes/Results
		Matched controls were given the same index-date and follow-up.	13) Sleep apnea, 14) BPD, 15) Traumatic injury, 16) Oxycodone and hydromorphone, 17) extended-release/long-acting opioids, 18) Max opioid MED 20–100 mg/daily 19) Benzodiazepines, antidepressants, and antipsychotics
Reference: Seal et al. 2012[8] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To investigate the effect of mental health disorders, particularly PTSD, on risks and adverse clinical outcomes associated with prescription opioid use. **Quality Rating:** Poor Statistical analysis of adverse events did not adjust for other potential confounding variables. Also, medical records could not verify medication adherence, and information on the specific pain diagnoses was lacking.	**Number of Patients:** 141,029 **Diagnosis:** Non-cancer-related pain **Age (Years):** Mean and range not reported **Gender:** 88.5% male **Inclusion Criteria:** Among veterans who entered VA health care from October 1, 2005, through December 31, 2008, the study enrolled Iraq and Afghanistan veterans who received a new non−cancer-pain diagnosis within 1 year of VA entry (n=141 029). Each veteran was followed up for 1 additional year from initial pain diagnosis to evaluate whether he/she received an opioid prescription and whether he/she experienced an adverse clinical outcome during this 1-year follow-up period. **Exclusion Criteria:** Not reported	15,676 patients received an opioid prescription for 20 or more consecutive days. The authors determined the prevalence of adverse clinical outcomes for veterans within each mental health diagnostic category (no mental health diagnosis, mental health diagnosis without PTSD, and PTSD with or without another mental health diagnosis) who were and were not prescribed opioids for pain. Because of the extremely large data set, they chose a p-value of <0.001 as a more conservative threshold for statistical significance. **Follow-up:** 1 year	**Adverse Clinical Outcomes (for patients using opioids)** **No PTSD (n=3205)** — **PTSD with or without another mental diagnosis (n=7983)** Wounds/ Injuries: 6.18% — 7.04% — p=0.11 Opioid-related accidents/ overdoses: 0.19% — 0.36% — p=0.19 Alcohol and nonopioid drug-related accidents/ overdoses: 0.81% — 2.25% — p<0.001 Self-inflicted injuries: 1.03% — 3.24% — p<0.001 Violence-related injuries: 0.53% — 0.76% — p=0.22 Findings were similar when comparing patients with PTSD (with or without other mental health diagnosis) to patients with no mental health diagnosis, except the prevalence of opioid-related accidents and overdoses was also significantly higher in the PTSD group (p<0.001). The study also found significantly higher rates (p<0.001) of opioid-related accidents and

Study Details	Patients/Interventions	Methods	Outcomes/Results
			overdoses, alcohol- and non-opioid drug-related accidents and overdose, and self-inflicted injuries in the non-PTSD mental disorders group compared to the group with no mental health diagnoses.
Reference: Bohnert et al. 2011[12] **Country:** USA **Study Design:** Case-cohort study **Purpose:** To examine the association of maximum prescribed daily opioid dose and dosing schedule ("as needed," regularly scheduled, or both) with risk of opioid overdose death among patients with cancer, chronic pain, acute pain, and substance use disorders. **Quality Rating:** Fair Appropriate case ascertainment (although some deaths could have been suicides misclassified as accidental overdoses), nonbiased selection of cases and controls, diagnostic procedures and measures applied equally to cases and controls, and all appropriate confounding variables were controlled for in multivariable analyses. Use of medical records may have resulted in under-detection of medical conditions.	**Number of Patients:** 155,434 **Diagnosis:** CNCP or cancer-related pain **Age (Years):** ≥18 years (mean and range not reported) **Gender:** 93.3% male **Inclusion Criteria:** The authors included two 5% random samples of VHA patients treated with opioids (one each for fiscal year [FY] 2004 and FY2005), as well as all FY2004 and FY2005 VHA patients who died of an opioid overdose before the end of FY2008 ("cases"). **Exclusion Criteria:** Individuals with indicators of palliative care consultations or hospice care in their VHA medical records were excluded.	The prescribed opioids included codeine, morphine, oxycodone, hydrocodone, oxymorphone and hydromorphone. Methadone was not included in the analysis because of its unique indications, duration of action, and inconsistent morphine equivalency. The authors developed Cox proportional hazards models to examine the relationship of opioid prescribing and risk of opioid overdose death adjusting for demographic and clinical characteristics. Multivariable modeling was restricted to periods when individuals were prescribed at least 1 opioid. Separate models were created for patients with CNCP (n=111,759), cancer pain (n=36,803), acute pain, and substance use disorders (these latter 2 were outside the scope of our analysis). Variables included in the models were opioid fill type, maximum prescribed daily dose, pain-related diagnoses, other diagnoses (SUD; psychiatric disorders; COPD, CVD, and sleep apnea), gender, age, and race. **Follow-up:** Mean length of follow-up not reported. For cases, observation time began on the date of the first opioid fill that occurred after the first medical visit within the study period to avoid potential immortal person-time. Similarly, for all non-cases, observation time began on the date of the first opioid fill that occurred after the first medical visit in the year for which the individuals were in the random sample. Observation time ended on the day of death or the end of FY2008, whichever came first.	**Cox Proportional Hazards Models of Risk of Death by Prescription Opioid Overdose** **Chronic Pain Patients**: Risk of overdose death was significantly increased with: 1) higher max prescribed daily opioid dose (HR 7.18, 95% CI: 4.85–10.65 for ≥100 mg/d vs. 1–20 mg/d), 2) SUD diagnosis (HR 2.53, 95% CI: 1.99–3.22), and 3) diagnosis of other psychiatric disorders (HR 1.87, 95% CI: 1.48–2.38). Risk was significantly decreased for: 1) age ≥50 categories, with lowest risk age ≥70 (HR 0.06, 95% CI: 0.02–0.18 vs. age 18–29 years), 2) in black patients vs. white patients (HR 0.37, 95% CI: 0.24–0.59), and 3) diagnosis of COPD, CVD or sleep apnea (HR 0.63, 95% CI: 0.50–0.80). **Cancer Patients:** Risk of overdose death was significantly increased with: 1) higher max prescribed daily opioid dose (HR 11.99, 95% CI: 4.42–32.56), 2) opioid prescription refills as needed (HR 2.75, 95% CI: 1.32–5.78 vs regularly scheduled refills), and 3) diagnosis of SUD (HR 3.08, 95% CI: 1.73–5.51). Risk was significantly decreased by age ≥60 years (HR 0.06, 95% CI: 0.01–0.64).

Study Details	Patients/Interventions	Methods	Outcomes/Results
			Higher opioid dose had the same association with overdose death in additional separate subgroups of patients with acute pain and SUDs.
Reference: Boscarino et al. 2010[11] **Country:** USA **Study Design:** Cross-sectional cohort study supplemented with retrospective database review **Purpose:** To assess the prevalence of and risk factors for opioid drug dependence among out-patients on long-term opioid therapy in a large health-care system. **Quality Rating:** Poor Low survey completion rate (33%), completers differed from non-completers in gender, marital status, smoking status, and general health. Case weights were developed to adjust for differences in participation by gender and clinic setting, but did not adjust for other differences. Diagnostic data were based on patient self-report. Multivariate regressions adjusted for most (but not all) relevant potential confounders. Some variables and outcomes were measured at the same time, so causality could not be determined.	**Number of Patients:** 705 **Diagnosis:** Non-cancer pain **Age (Years):** ≥18 years, but mean and range not reported **Gender:** Not reported **Inclusion Criteria:** Patients were eligible for this study if they were 18+ years of age, received care from one of nine community practice clinics or from the three specialty clinics, including a pain management, orthopedics and a rheumatoid clinic, and were prescribed opioid medications 4+ times for non-malignant pain any time from 30 June 2006 to 1 July 2007. **Exclusion Criteria:** Of patients contacted by phone, 234 were determined to be ineligible for study, due to death, institutionalization, language barriers, illness, denial of opioid use or due to being in the last survey batch not contacted because the study quota was completed.	Patients who met inclusion criteria underwent structured diagnostic interviews that included: (i) a modified CIDI; (ii) assessment of depression, PTSD, general anxiety and psychological trauma using a diagnostic interview designed for this purpose; and (iii) questions relevant to severity of opioid dependence, tobacco dependence, and childhood neglect. Substance misuse and dependence were defined using DSM-IV criteria. Response bias was analyzed using EHR data to compare study respondents (n=705) to eligible non-respondents (n=1434). These results led to development of weights to adjust for potential response bias. Logistic regressions were used to identify risk factors for opioid dependence. To identify useful models, only variables with bivariate p-values <0.10 were selected. In addition, only variables that remained significant at p<0.10 were retained in the final multivariate models. **Follow-up:** Outcomes were measured at time of interview, while some risk factor data came from medical records covering the past 3 years prior to the interview.	**Model 1: Life-time Opioid Dependence** Life-time opioid dependence was associated with: 1) age <65 (OR=2.80, p<0.001), 2) current pain impairment (OR=1.94, p=0.01), 3) history of opioid abuse (OR=3.95, p<0.001), 4) higher life-time opioid dependence severity (OR=3.00, p=0.003), 5) higher numbers of opioid orders (OR=1.75, p=0.009) and 6) history of antisocial personality disorder (OR=1.44, p=0.015). **Model 2: Current Opioid Dependence** Current opioid dependence was associated with 1) age <65 (OR=2.33, p=0.001), 2) history of opioid abuse (OR=3.81, p<0.001), 3) higher life-time opioid dependence severity (OR=1.85, p=0.001), 4) history of major depression (OR=1.29, p=0.022) and 5) psychotropic medication use (OR=1.73, p=0.006).

* Estimated from Figure 2 presented in the study

ANCOVA: analysis of covariance; AOR: adjusted odds ratio; BPD: borderline personality disorder; BPI: brief pain inventory; BTDS: buprenorphine transdermal system; CHF: congestive heart failure; CI: confidence interval; CIDI: composite international diagnostic interview; CLBP: chronic low back pain; CNCP: chronic non-cancer pain; COPD: chronic obstructive pulmonary disease; COT: chronic opioid therapy; CPT: current procedural terminology; CSA: chronic short-acting; CVD: cardiovascular disease; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ED: emergency department; EHR: electronic health record; FY: fiscal year; GAD: generalized anxiety disorder; GH: group health; HIV: human immunodeficiency virus; HR: hazard ratio; ICD: International Statistical Classification of Diseases and Related Health Problems'; IPDE: International Personality Disorder Examination; KPCO: Kaiser Permanente Colorado; LA: long-acting; LBP: low back pain; LMM: linear mixed modeling; MED: morphine equivalent dose; MOS-SS SOBH: medical outcomes study sleep scale, awakening due to shortness of breath or headache; NA: negative affect; OME: oral morphine equivalents; OUD: opioid use disorder; OR: odds ratio; POINT: pain and opioids in treatment; PSEQ: pain self-efficacy questionnaire; PTSD: posttraumatic stress disorder; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; SNRI: serotonin-norepinephrine reuptake inhibitor; SUD: substance use disorder; TdP: torsades de pointes; THC: tetrahydrocannabinol; TOA: therapeutic opioid addiction; UDT: urine drug test; VHA: Veteran's Health Administration

Appendix B. References

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Appendix C. Excluded Studies

Table 3. Excluded Studies

Reference	Reason for Exclusion
Agarin et al. 2015[17]	Upon reviewing full text: Does not address a key question
Annemans 2011[18]	Upon reviewing full text: Does not address a key question
Arteta et al. 2015[19]	Study used surrogate outcome (COMM risk score) to assess opioid misuse risk
Barth et al. 2014[20]	Study used surrogate outcome (COMM risk score) to assess opioid misuse risk
Brennan and Lieberman III 2016[21]	Narrative review, all included studies published pre-2009
Chipchase et al. 2012[22]	Upon reviewing full text: Does not address a key question
Cicero et al. 2009[23]	Analysis inadequate to address the question
Crocker et al. 2014[24]	Population not of interest
Dennis et al. 2015[25]	Upon reviewing full text: Does not address the key question
Fishbain et al. 2011[26]	Pain outcomes measured at <12 weeks
Ghate et al. 2010[27]	Not a systematic review or clinical trial of any design (e.g. narrative review, opinion paper, previous guideline)
Green et al. 2011[28]	Condition is substance abuse, study does not report on pain diagnoses
Hojsted et al. 2012[29]	Narrative review of 2 other reviews from 2009 and 2010
Hooten et al. 2010[30]	Upon reviewing full text: Does not address a key question
Jamison et al. 2013[31]	Post hoc analysis with >50% attrition
Johnson et al. 2012[32]	Case-control with inappropriate control group
Jungquist et al. 2012[33]	Upon reviewing full text: Does not address a key question
Kidner et al. 2010[34]	Does not report on an outcome of interest (refer to protocol)
Makris et al. 2015[35]	Upon reviewing full text: Does not address a key question
Marschall et al. 2015[36]	Does not separate opioids from other drug hospitalizations in multivariate analyses
Morasco et al. 2011[37]	Does not report on an outcome of interest (refer to protocol)
Morasco et al. 2013[38]	Study uses risk scores instead of specific variables to predict outcomes
Morasco et al. 2011[39]	The only included studies relevant to KQ 1 were mostly poor quality, most would not have met our inclusion criteria, and all were published prior to 2009.
Morasco et al. 2014[40]	Does not report on an outcome of interest (refer to protocol)
Page et al. 2015[41]	Study uses risk scores instead of specific variables to predict outcomes
Sekhon et al. 2013[42]	Retrospective study with no multivariate analysis
Skinner et al. 2012[43]	Cross-sectional study with no relevant outcomes
Webster et al. 2008[44]	Published in 2008, included in 2010 VA-DoD guideline.
Zedler et al. 2014[13]	Analysis does not separate acute from chronic pain or short-term from chronic opioid use

Key Question 2: What factors increase the risk of developing misuse or OUD when considering COT?

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Key Question 2: What factors increase the risk of developing misuse or OUD when considering COT?

Summary of Evidence Base

Our literature searches identified 12 studies (mostly retrospective or prospective cohort studies) that provided potential evidence concerning risk factors for developing misuse or OUD. Because there is extensive overlap among studies that address KQ 1 and 2, the data concerning medical and mental health conditions as potential risk factors for aberrant drug behaviors (including opioid misuse, dependence and overdose) appears only in the summary for KQ 1. The summary for KQ 2 focuses on other potential risk factors (e.g., opioid dose, age, and other non-medical variables). The included studies evaluated the following risk factors and their association with negative outcomes in chronic pain patients receiving opioid therapy.

- Opioid dose
    - Opioid dependence/OUD: Two retrospective cohort studies found significant associations between increasing opioid dose and increased risk of opioid dependence or OUD. The largest study found that the effect varied by average daily dose and number of days supplied (days' supply). Dose had a larger effect with COT, but even a low dose combined with COT had a strong association with OUD (Quality of evidence: Moderate).
    - Aberrant urine drug test (UDT) or non-adherence: One retrospective cohort study reported that patients on moderate opioid dosage (40 to <120 mg daily) had a significantly lower risk of aberrant results than patients at low daily dosage (<40 mg daily). This may be explained by the fact that the most frequent aberrant event was prescribed opioid non-detection (indicating non-adherence). Patients on moderate or high dosage opioids had significantly lower risk of prescribed opioid non-detection than patients on low dosage (Quality of evidence: Moderate).
    - Opioid-related respiratory/CNS depression or overdose: One case-control study found that a maximum prescribed daily opioid morphine equivalent dose (MED) ≥100 mg/day was significantly associated with opioid-related toxicity/overdose (Quality of evidence: Low).
    - Overdose: Two retrospective cohort studies found a significant association between ≥100 mg daily opioid dose and increased risk of overdose (a slightly smaller but significant association was found for 50–99 mg/day opioid dose and overdose) (Quality of evidence: Moderate).
    - Overdose death: One large case-cohort study found that risk of overdose death was significantly increased with increasing maximum prescribed daily opioid dose, while a retrospective cohort study found that patients who escalated to high dose opioid therapy (>200 mg/day) were nearly 24 times as likely to die as those who did not escalate (Quality of evidence: Moderate).
- Opioid duration
    - Opioid dependence/OUD: The best evidence came from a large retrospective cohort study which showed that chronic (versus acute) opioid prescription had a strong association with risk of OUD, regardless of opioid dose (Quality of evidence: Moderate).

- Any aberrant result (from UDT): One retrospective cohort study found that days' supply of opioids was not significantly associated with any aberrant result (Quality of evidence: Moderate).
- Non-adherence: The same study found that prescribed opioid non-detection was slightly less common among patients with daily/near-daily opioid supply versus less-than-daily supply, although this association was weak (Quality of evidence: Moderate).
- Non-prescribed opioids: The same study also found that non-prescribed opioids were weakly associated with excessive (versus less than-daily) opioid supply (Quality of evidence: Moderate).

- Opioid prescription refill type
  - Opioid-related overdose death: One large case-cohort study reported that opioid refill type was not significantly associated with overdose death in patients with CNCP, but a significant association was found among cancer patients between as needed refill (versus regularly scheduled refill) and overdose death (Quality of evidence: Moderate).
- Age
  - Opioid dependence/OUD: Four out of five cohort studies found a significant association between younger age and increased risk of opioid dependence or OUD (the studies used different age subgroups and cutoffs for their analyses) (Quality of evidence: Moderate).
  - Any aberrant result, non-adherence, and non-prescribed opioids (from UDT): One retrospective cohort study found that any aberrant result was significantly less common among patients age 45–64 years (a weak association) and 65+ years (a stronger association) versus patients aged 20–44 years. The same association patterns were found for prescribed opioid non-detection and detection of non-prescribed opioids (Quality of evidence: Moderate).
  - Opioid-related respiratory/CNS depression or overdose: One case-control study found that opioid-related toxicity or overdose was weakly associated with older age groups (age 55–64 and 65+ years versus 18–34 years (Quality of evidence: Low).
  - Overdose death: One large case-cohort study reported that risk of overdose death was significantly decreased in age ≥50 categories, with lowest risk for age ≥70 years (Quality of evidence: Moderate).
- Gender
  - Opioid dependence/OUD: Three out of five studies found a significant (but relatively weak) association between male gender and risk of opioid dependence/OUD. Of the two studies that did not, one was low quality and one was small enough that it may have lacked statistical power to detect a small association (Quality of evidence: Low).
  - Any aberrant result (from UDT): One retrospective cohort study found that male gender was weakly associated with more aberrant UDT results (Quality of evidence: Moderate).
  - Non-adherence or non-prescribed opioids (from UDT): The same study also found that male gender was not significantly associated with prescribed opioid non-detection (OR=1.16; 95% CI: 0.96–1.40) or detection of non-prescribed opioids (Quality of evidence: Moderate).

- Overdose death: One retrospective cohort study reported that men were twice as likely as women to experience an opioid-related death (Quality of evidence: Moderate).

- Pain interference or impairment
  - Opioid dependence: One cross-sectional cohort study reported that pain interference was significantly associated with 12-month opioid dependence in univariate but not in multivariate analyses, while another cross-sectional study reported that current pain impairment was weakly associated with lifetime opioid dependence, but not current opioid dependence in multivariate analyses (Quality of evidence: Very Low).

- Race
  - Any aberrant result and non-adherence (from UDT): One retrospective cohort study found that race was not significantly associated with any aberrant result or with prescribed opioid non-detection (Quality of evidence: Moderate).
  - Non-prescribed opioid (from UDT): The same study reported that non-prescribed opioids were significantly more common among African-American patients than white patients (Quality of evidence: Moderate).
  - Opioid-related respiratory/CNS depression or overdose: One case-control study found that opioid-related toxicity or overdose was weakly associated with being non-Hispanic white (versus non-Hispanic black) (Quality of evidence: Low).
  - Overdose death: One large case-cohort study reported that risk of overdose death was significantly decreased in black patients compared to white patients (Quality of evidence: Moderate).

- Marital status
  - Opioid dependence: One cross-sectional cohort study found that marital status was not significantly associated with opioid dependence (Quality of evidence: Low).
  - Opioid-related respiratory/CNS depression or overdose: One case-control study found that opioid-related toxicity or overdose was significantly associated with being widowed and weakly associated with being never married (versus married) (Quality of evidence: Low).

- Employment status
  - Opioid dependence: One cross-sectional cohort study found that unemployment was not significantly associated with opioid dependence in multivariate analyses (Quality of evidence: Very Low).

- Health care utilization
  - Opioid-related respiratory/CNS depression or overdose: One case-control study found that days of hospitalization (≥1 versus none) was significantly associated with opioid-related toxicity or overdose (Quality of evidence: Low).

Overview of Evidence Base

Our searches identified 12 individual studies (in 13 publications) that addressed this key question. These were primarily cohort studies (prospective,[1] retrospective[2-9] or cross-sectional[10,11]) with the exception of one case-cohort study[12] and one nested case-control study.[13] Each study evaluated associations between potential risk factors and opioid misuse or OUD in opioid-treated patients with chronic non-cancer pain (CNCP); the case-cohort study also separately evaluated patients with cancer-related pain. Because there is extensive overlap among studies that address KQ 1 and 2, the data concerning medical and mental health conditions as potential risk factors for aberrant drug behaviors (including opioid misuse, dependence and overdose) appears only in the summary for KQ 1. The summary for KQ 2 focuses on other potential risk factors (e.g., opioid dose, age, and other non-medical variables). Excluded studies and the reasons for exclusion appear in Table 3 (Appendix C).

Study Quality Rating

Because the USPSTF does not have criteria specific for evaluation of prognostic studies, we rated the quality of the majority of studies using the recently-developed Quality in Prognosis Studies tool.[14] The majority of prospective and retrospective cohort studies were rated as Fair quality using this instrument. The main limitation of these studies was that not all potential confounding variables were adjusted for in statistical analyses, which leaves doubt concerning the strength of any observed associations between a risk factor and a treatment outcome. One prospective cohort study was rated as Poor quality because there was no statistical adjustment for potential confounders, high attrition, and missing patients were significantly younger than those who completed follow-up.

Cross-sectional cohort studies were rated as Poor quality because, in addition to having this same limitation, the measurement of all variables and outcomes at the same time point precluded assessment of causality (i.e., that a prognostic factor preceded outcome occurrence). Also, there were differences or potential differences between enrolled patients and those who were eligible but did not participate.

The case-cohort study (Bohnert et al.[12]) and the nested case-control study (Nedler et al.[13]) were rated using USPSTF criteria for case-control studies. Bohnert et al. was rated as Fair quality because of slight limitations in use of medical records data and a small possibility of case misclassification. Nedler et al. was rated as Poor quality because the study did not report the percentage of patients with acute versus chronic pain or the percentage of patients receiving short-term opioid therapy versus COT.

Overview of Study, Patient, and Intervention Characteristics

Campbell et al. (2015) conducted two analyses of data from a cross-sectional cohort study. The first analysis included 1,424 patients with CNCP who had received prescription opioids for more than six weeks (patients taking methadone or buprenorphine as opioid substitution therapy for heroin dependence were excluded). The median patient age was 58 years and 55% were female. The study used univariate and multivariate regression analyses to identify factors associated with past year pharmaceutical opioid dependence. These included (among others) various substance abuse diagnoses, aberrant behaviors, and mental health conditions.[10]

Huffman et al. (2015) conducted a retrospective cohort study that included 199 patients who had undergone long-term opioid therapy for CNCP. The mean age was 46.5 years and 60.8% of patients were female. The

study used logistic regression to determine whether history of non-opioid substance usage or OME dosage at time of admission increased the risk of therapeutic opioid addiction.[15]

Kaplovitch et al. (2015) performed a retrospective cohort study of 32,449 patients receiving COT for non-cancer pain. The median patient age was 47 years for men and 44 years for women; 58% of patients were women. The authors used Cox proportional hazards regression to estimate the risks of dose escalation and opioid-related mortality for men relative to women, after adjusting for all other variables with a standardized difference greater or equal to 0.10. Patients were followed from their first opioid prescription until discontinuation of opioid treatment, death, or the end of the study period (average follow-up not reported).[3]

Turner and Liang (2015) conducted a retrospective cohort study of 206,869 HMO patients with CNCP who received at least two Schedule II or III prescriptions for non-injectable opioid analgesics from January 2009 through July 2012. The mean patient age was 44.1 years (range 18 to 64 years) and 57% were female. The study used repeated measures logistic regression to evaluate interactions of filled prescriptions (including opioids, benzodiazepines, antidepressants, and zolpidem) with mental health disorders (anxiety/PTSD, depression, and psychotic disorder) in regard to drug overdose. Other factors included in the analyses were age, gender, region, SUD, clinical conditions, and opioid dose. Patients were followed for up to 3.5 years.[4] The authors presented additional relevant data from this study in a separate publication.[5]

Edlund et al. (2014) conducted a retrospective cohort study of 568,640 patients with a new episode of a CNCP condition; the dataset was derived from a health plan database (HealthCore). All patients were at least 18 years old (mean age not reported) and 58% were female. The authors used logistic regression analysis to investigate the association between exposure to prescription opioids and incident opioid use disorders (OUDs). Other covariates in the adjusted analyses included opioid dose and number of days supplied, age in years, gender, number of types of tracer pains in the pre-index period, number of non-tracer pain categories, number of non-substance mental health disorder types, pre-index substance abuse/dependence diagnoses, and Charlson score. The outcome of interest was any diagnosis of an OUD (opioid abuse or dependence) occurring in the 18-month period after the index date.[6]

Turner et al. (2014) conducted a retrospective cohort study of 3,809 primary care patients on COT who underwent urinary drug testing (UDT). Patients were at least 20 years old (mean and range not reported) and 60.6% were female. Factors were evaluated in univariate logistic regression analyses to identify associations with aberrant UDT results. All predictors were entered in a multivariable model for each outcome that had sufficient counts for reliable results. Patient visit diagnoses were identified within 2 years prior to the index UDT.[7]

Zedler et al. (2014) conducted a retrospective nested case-control study of 8,987 veterans who received at least one opioid prescription from VHA during a two-year time period. The median patient age was 62 years and 92.1% were male. The “cases” were patients who had at least one opioid-related respiratory/CNS depression event or overdose during the study period. Each case was matched with 10 randomly selected controls who had received opioids during the same period but did not experience opioid-related toxicity or overdose. The authors used multivariable logistic regression to identify factors associated with a case event. The baseline period covered six months prior to the index event. For cases, the follow-up period was calculated as the number of days after the end of the event until death, disenrollment, or the end of the study period. Matched controls were given the same index-date and follow-up.[13]

Bohnert et al. (2011) conducted a case-cohort study of 155,434 veterans treated with prescription opioids for CNCP, cancer, acute pain, and SUD. Only the first two groups were within the scope of our review, and the authors performed separate analyses for each patient subgroup. All patients were at least 18 years old (mean age was not reported) and 93.3% were male. The authors used Cox proportional hazards models to evaluate the association of opioid dose and dosing schedule with risk of opioid overdose death. Other factors included in the models were pain-related diagnoses, other diagnoses (SUD; psychiatric disorders; COPD, CVD, and sleep apnea), gender, age, and race. The mean length of follow-up was not reported.[12]

Boscarino et al. (2010) performed a cross-sectional cohort study of 705 patients who received at least four opioid prescriptions for non-cancer pain over a one-year period. Mean patient age and gender were not reported. Patients underwent structured diagnostic interviews that included a modified Composite International Diagnostic Interview (CIDI); substance misuse and dependence were defined using DSM-IV criteria collected by the CIDI instrument. The authors used univariate and multivariate logistic regression to identify risk factors for opioid dependence. Variables assessed as potential risk factors included age, gender, current psychotropic drug use, various mental health conditions, and history of substance use/dependence (opioids, alcohol, illicit drugs, and smoking were separate variables). Outcomes were measured at time of interview, while some risk factor data came from medical records covering the past 3 years prior to the interview.[11]

Dunn et al. (2010) conducted a retrospective cohort study of 9,940 patients with CNCP initiating a new episode of opioid use (with three or more opioid prescriptions in the first 90 days of the episode). The mean patient age was 54 years (range 18 to 99 years), and 59.6% were female. The authors employed a Cox proportional hazards model to estimate the risk of overdose across individuals as a function of their average daily opioid dose, with sedative hypnotic use included as a time-varying covariate. Hazard ratios for these variables were adjusted for other non-time-varying covariates. Patients were followed for a mean of 42 months (range <1 to 119 months) from their initial 90-day exposure window.[8]

Jamison et al. (2010) performed a prospective cohort study of 610 patients with CNCP and an opioid prescription. The mean patient age was 50.4 years and 54.8% were women. The authors evaluated gender differences using a range of instruments (see Table 2) to measure aberrant drug-related behavior (misuse or abuse). The follow-up period was five months.[1]

Banta-Green et al. (2009) conducted a retrospective cohort study of 704 patients with CNCP receiving COT. The mean age ranged from 52 to 56 years in different patient subgroups, and 49% to 65% were female. The authors used latent class analysis to identify three subgroups of patients based on addictive behaviors and pain treatment problems: the three classes were typical, addictive behaviors, and pain dysfunction, respectively. Multivariate regression was used to identify associations between potential risk factors (identified through automated and interview data) and the most likely patient class. Automated data provided diagnostic and prescription information within three years prior to patient interviews.[9]

Outcomes and Synthesis of Results

Below we summarize the results of the evidence base that evaluated potential associations between risk factors and outcomes related to opioid misuse or OUD. For additional information on study results see Tables 1 and 2. As noted for the previous key questions, many epidemiologists consider odds ratios (ORs) and relative risks (RR) of less than 3, and especially less than 2, in observational studies as weak or very weak associations that could be explained by confounding or even chance.

Opioid Dose

Opioid dependence/OUD: Two retrospective cohort studies found significant associations between increasing opioid dose and increased risk of opioid dependence or OUD. The largest study (Edlund et al.) found that the effect varied by average daily dose and days' supply. Dose had a larger effect with COT, but even a low dose combined with COT had a strong association with OUD: low dose, chronic (OR=14.92; 95% CI: 10.38 to 21.46); medium dose, chronic (OR=28.69; 95% CI: 20.02 to 41.13); high dose, chronic (OR=122.45; 95% CI: 72.79 to 205.99).[6] Huffman et al. found that each 10-mg increase of oral morphine was associated with a 12% increase in odds of therapeutic opioid addiction (OR=1.12; 95% CI: 1.05 to 1.18); each 50-mg increase was associated with a 73% increase in the odds (OR=1.73; 95% CI: 1.29 to 2.32); and each 100-mg increase was associated with a 3-fold increase in the odds (OR=3.00; 95% CI: 1.67 to 5.41).[2]

Addictive behaviors: Banta-Green et al. found that higher average prescribed daily dose opioids was significantly associated with patients in the addictive behaviors and pain dysfunction groups (ORs 3.67 and 6.18, respectively).[9]

Any aberrant result (from UDT) or non-adherence: Turner et al. reported that patients on moderate opioid dosage (40 to <120 mg daily) had a lower risk of aberrant results than patients at low daily dosage (<40 mg daily) (HR=0.78; 95% CI: 0.65 to 0.95). This may be explained by the fact that the most frequent aberrant event was prescribed opioid non-detection (indicating non-adherence). Patients on moderate or high dosage opioids had significantly lower risk of prescribed opioid non-detection than patients on low dosage (HR=0.52 and 0.22, respectively).[7]

Opioid-related respiratory/CNS depression or overdose: Zedler et al. found that a maximum prescribed daily opioid MED ≥100 mg/day was significantly associated with opioid-related toxicity/overdose (HR=4.1; 95% CI: 2.6 to 6.5).[13]

Overdose: Two retrospective cohort studies found a significant association between ≥100 mg daily opioid dose and increased risk of overdose. Liang and Turner reported that the strongest associations with drug overdose were observed for ≥100 mg daily opioid dose regardless of total dose or 50 to 99 mg daily dose combined with a high total dose (>1,830 mg).[5] Dunn et al. found that overdose risk increased nine-fold for high dose opioids (≥100 mg/day) versus the lowest opioid doses.[8]

Opioid-related death: Bohnert et al. found that risk of overdose death was significantly increased with increasing maximum prescribed daily opioid dose (HR=7.18; 95% CI: 4.85 to 10.65 for ≥100 mg/d versus 1–20 mg/d).[12] Kaplovitch et al. reported that patients who escalated to high dose opioid therapy (>200 mg/day) were nearly 24 times as likely to die as those who did not escalate (3.1% vs. 0.1%, respectively).[3]

Opioid Duration

Opioid dependence/OUD: Edlund et al. found that opioid prescription was associated with significantly more OUD, and the effect varied by average daily dose and days' supply. Longer duration (chronic) seemed to greatly increase the risk of OUD and this was particularly strong at high dosage. The combinations of dose and duration were as follows: low dose, acute (OR=3.03; 95% CI: 2.32, 3.95), low dose, chronic (OR=14.92; 95% CI: 10.38 to 21.46), medium dose, acute (OR=2.80; 95% CI: 2.12 to 3.71), medium dose, chronic (HR=28.69; 95% CI: 20.02 to 41.13), high dose, acute (HR=3.10; 95% CI: 1.67 to 5.77), and high dose, chronic (OR=122.45; 95% CI: 72.79 to 205.99).[6] Boscarino et al. reported that life-time opioid dependence was weakly associated with higher numbers of opioid orders (OR=1.75, p=0.009), while opioid orders were not a significant factor in the final multivariate model for current opioid dependence.[11]

Any aberrant result (from UDT): Turner et al. found that days' supply of opioids was not significantly associated with any aberrant result (OR=0.88; 95% CI: 0.75 to 1.04 for daily/near daily supply versus less than daily supply).[7]

Non-adherence: The same study found that prescribed opioid non-detection was slightly less common among patients with daily/near-daily opioid supply versus less-than-daily supply (OR=0.78; 95% CI: 0.63 to 0.96), although this association was weak.[7]

Non-prescribed opioids: Turner et al. also found that non-prescribed opioids were weakly associated with excessive (versus less than-daily) opioid supply (OR=1.59; 95% CI: 1.03 to 2.46).[7]

Opioid Prescription Refill Type (Regularly Scheduled, As Needed, or Both)

Opioid-related overdose death: Bohnert et al. reported that opioid refill type was not significantly associated with overdose death in patients with CNCP, but a significant association was found among cancer patients (HR=2,75; 95% CI: 1.31 to 5.78 for as needed refill versus regularly scheduled refill).[12]

Age

Opioid dependence/OUD: Five cohort studies evaluated a potential association between age and opioid dependence/OUD.[2,6,9-11] Four out of five studies (including the largest study by Edlund) found a significant association between younger age and increased risk of opioid dependence or OUD (the studies used different age subgroups and cutoffs for their analyses). Edlund found the highest risk in the 18–30 years' subgroup (OR=10.51 versus age 65+).[6] The smallest study (Huffman) was the only study that did not find a significant association,[2] and it may have lacked adequate statistical power.

Any aberrant result (from UDT): Turner et al. found that any aberrant result was significantly less common among patients age 45–64 years (OR=0.77; 95% CI: 0.65 to 0.92, a weak association) and 65+ years (OR=0.40; 95% CI: 0.32 to 0.50) versus patients aged 20–44 years.[7]

Non-adherence (from UDT): Turner et al. found significant reductions in prescribed opioid non-detection among the 45–64 (OR=0.79; 95% CI: 0.63 to 0.998, a weak association) and 65+ years age groups (OR=0.44; 95% CI: 0.32 to 0.59) versus patients aged 20–44 years.[7]

Non-prescribed opioids (from UDT): Turner et al. found significant reductions in detection of non-prescribed opioids among the 45–64 (OR=0.52; 95% CI: 0.38 to 0.70) and 65+ years age groups (OR=0.44; 95% CI: 0.30 to 0.65) versus patients aged 20–44 years.[7]

Opioid-related respiratory/CNS depression or overdose: Zedler et al. found that opioid-related toxicity or overdose was weakly associated with older age groups: age 55–64 (OR=1.9; 95% CI: 1.1 to 3.3) and 65+ years (OR=1.8; 95% CI: 1.1 to 3.2) vs.18–34 years.[13]

Overdose death: Bohnert et al. reported that risk of overdose death was significantly decreased in age ≥50 categories, with lowest risk for age ≥70 (HR=0.06; 95% CI: 0.02 to 0.18 versus age 18–29 years).

Gender

Opioid dependence/OUD: Three out of five studies (including the largest study by Edlund) found a significant (but relatively weak) association between male gender and risk of opioid dependence/OUD.[1,6,9] Of the two studies that did not, one was low quality[10] and one was small enough that it may have lacked statistical power to detect a small association.[2]

Any aberrant result (from UDT): Turner et al. found that male gender was weakly associated with more aberrant UDT results (OR=1.24; 95% CI: 1.07 to 1.43).[7]

Non-adherence or non-prescribed opioids (from UDT): Turner et al. also found that male gender was not significantly associated with prescribed opioid non-detection (OR=1.16, 95% CI: 0.96 to 1.40) or detection of non-prescribed opioids (OR=1.03; 95% CI: 0.77 to 1.38).[7]

Overdose death: Kaplovitch et al. reported that men were twice as likely to experience an opioid-related death (adjusted HR=2.04; 95% CI: 1.18 to 3.53) compared to women.[3]

Pain Interference or Impairment

Opioid dependence: Campbell et al. reported that pain interference was significantly associated with 12-month opioid dependence in univariate but not in multivariate analyses (Adj RR=1.05; 95% CI: 0.91 to 1.21). Pain severity was not associated with dependence in any analysis.[10] Boscarino et al. found that current pain impairment was weakly associated with lifetime opioid dependence (OR=1.94; p=0.01), but not current opioid dependence in multivariate analyses.[11]

Race

Any aberrant result (from UDT): Turner et al. found that race was not significantly associated with any aberrant result (OR=1.13; 95% CI: 0.81 to 1.56).[7]

Non-adherence (from UDT): Turner et al. also found that race was not significantly associated with prescribed opioid non-detection (OR=1.14; 95% CI: 0.76 to 1.72).[7]

Non-prescribed opioid (from UDT): Turner et al. reported that non-prescribed opioids were significantly more common among African-American patients than white patients (OR=2.07; 95% CI: 1.16 to 3.69).[7]

Opioid-related respiratory/CNS depression or overdose: Zedler et al. found that opioid-related toxicity or overdose was weakly associated with being non-Hispanic white (versus non-Hispanic black) (OR=1.8, 95% CI: 1.3 to 2.4).[13]

Overdose death: Bohnert reported that risk of overdose death was significantly decreased in black patients (HR=0.37; 95% CI: 0.24 to 0.59) compared to white patients.[12]

Marital Status

Opioid dependence: Campbell et al. found that marital status was not significantly associated with opioid dependence.[10]

Opioid-related respiratory/CNS depression or overdose: Zedler et al. found that opioid-related toxicity or overdose was significantly associated with being widowed (OR=2.0; 95% CI: 1.4 to 3.0) and weakly associated with being never married (OR=1.4; 95% CI: 1.0 to 1.8) versus married.[13]

Employment Status

Opioid dependence: Campbell et al. found that unemployment was not significantly associated with opioid dependence in multivariate analyses (OR=1.31; 95% CI: 0.73 to 2.33).[10]

Health Care Utilization

Opioid-related respiratory/CNS depression or overdose: Zedler et al. found that days of hospitalization (≥1 versus none) was significantly associated with opioid-related toxicity or overdose (OR=2.9; 95% CI: 2.3 to 3.6).[13]

Overall Quality of Evidence Rating

Opioid Dose

The overall quality of evidence for associations between opioid dose and opioid misuse/OUD was Moderate (due to serious study limitations) for most outcomes (opioid dependence/OUD, aberrant UDT results, non-adherence, drug overdose, and opioid-related death), the exception being a combined outcome of opioid-related toxicity overdose (Low-quality evidence from one study with very serious limitations). In general, higher opioid doses (particularly opioid dose ≥100 mg/day) were consistently associated with increased risk of negative outcomes, with the exception of non-adherence (more common among patients on low doses).

Opioid Duration

The overall quality of evidence was Moderate (due to serious study limitations) for a significant association between opioid duration and opioid/dependence OUD. The best evidence came from a large retrospective cohort study which showed that chronic (versus acute) opioid prescription had a strong association with risk of OUD, regardless of opioid dose.

Opioid Prescription Refill Type (Regularly Scheduled, As Needed, or Both)

The quality of evidence was Moderate (based on one large case-cohort study with serious limitations) that opioid refill type was not significantly associated with overdose death in patients with CNCP. However, the same study did find a significant association in a separate group of patients with cancer.

Age

The overall quality of evidence was Moderate (based on five studies with serious limitations and three studies with very serious limitations) for almost all outcomes and supported a significant association

between younger age and increased risk of opioid dependence/OUD, aberrant results, non-adherence, opioid-related toxicity/overdose, and overdose-related death.

Gender

The quality of evidence concerning gender ranged from Low (for opioid dependence/OUD) to Moderate (for any aberrant result, non-adherence, non-prescribed opioid use, and overdose-related death). The Low quality rating stemmed from serious study limitations and inconsistency in the findings (which showed no association or a weak association with male gender as a risk factor) among the five studies that evaluated gender and opioid dependence/OUD. A Moderate rating represented only serious study limitations, but the remaining outcomes also showed either no significant association or a weak association with male gender as a risk factor.

Pain Interference or Impairment

The quality of evidence was Very Low (due to serious inconsistency in the findings of two studies with very serious limitations) concerning an association between pain interference or impairment and opioid dependence. One study found no significant association between pain interference and opioid dependence in a multivariate analysis, while the other found a weak association between current pain impairment and lifetime opioid dependence (but not current opioid dependence).

Race

The quality of evidence evaluating an association between race and opioid misuse/OUD ranged from Low to Moderate for different outcomes. Moderate-quality evidence from one study with serious limitations suggested no significant association between race and aberrant UDT results or non-adherence, although it did find a significant association between being African-American and having a higher rate of non-prescribed opioid use. Low-quality evidence from one study with very serious limitations suggested that risk of opioid-related toxicity/overdose was weakly associated with being non-Hispanic white. Similarly, Moderate-quality evidence from one study with serious limitations found that risk of overdose death was significantly decreased in black patients (versus white patients).

Marital Status

The overall quality of evidence was Low based on two studies with very serious limitations. One study found that marital status was not significantly associated with opioid dependence, while the other found a significant association between opioid-related toxicity/overdose and being widowed or never married (the latter association was weak).

Employment Status

The quality of evidence was Very Low based on one study with very serious limitations and serious imprecision in the effect estimate. It found that unemployment was not significantly associated with opioid dependence.

Health Care Utilization

The quality of evidence was Low based on one study with very serious limitations that found days of hospitalization (≥1 versus none) was significantly associated with opioid-related toxicity or overdose.

Table 1. Overall Assessment of Quality of Evidence Base

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Opioid Dose								
Opioid dependence/ OUD	2 retrospective cohort studies (Huffman et al. 2015;[2] Edlund et al. 2014[6])	Prescription opioids (Huffman: 199 patients) mean MED 132.85, SD 175.39 mg/day; (Edlund: 568,640 patients), MED range 0 to >120 mg/day	Huffman: Each 10-mg increase of oral morphine was associated with a 12% increase in odds of TOA (OR=1.12; 95% CI: 1.05 to 1.18). Each 50-mg increase was associated with a 73% increase in odds of TOA (OR=1.73; 95% CI: 1.29 to 2.32). Each 100-mg increase was associated with 3-fold increase in odds of TOA (OR=3.00; 95% CI: 1.67 to 5.41). Edlund: Opioid prescription was associated with significantly more OUD, and the effect varied by average daily dose and days' supply. Dose had a larger effect with COT: low dose, chronic (OR=14.92; 95% CI: 10.38, 21.46); medium dose, chronic (OR=28.69; 95% CI: 20.02, 41.13); high dose, chronic (OR=122.45; 95% CI: 72.79, 205.99)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Addictive behaviors	1 retrospective cohort study (Banta-Green et al. 2009)[9]	Prescription opioids (704 patients); mean MED 50 (±64) mg/day	Higher average prescribed daily dose opioids was significantly associated with patients in the addictive behaviors and pain dysfunction groups (ORs 3.67 and 6.18, respectively)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Any aberrant result (from UDT)	1 retrospective cohort study (Turner et al. 2014)[7]	Prescription opioids (3,809 patients); MED range <40 mg/day to >120 mg/day (67.4% of patients received <40 mg/day)	Patients on moderate opioid dosage (40 to <120 mg daily) had a lower risk of aberrant results than patients at low daily dosage (<40 mg daily) (OR=0.78; 95% CI: 0.65–0.95)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Non-adherence (from UDT)			Patients on moderate or high dosage opioids had significantly lower risk of prescribed opioid non-detection than patients on low dosage (ORs 0.52 and 0.22, respectively).					
Opioid-related respiratory/ CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases: 98.7 mg/day; for controls: 24.2 mg/day	Max prescribed daily opioid MED ≥100 mg/day was significantly associated with opioid-related toxicity/overdose (OR=4.1; 95% CI: 2.6-6.5).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Drug overdose	2 retrospective cohort studies (Turner and Liang 2015;[4] Liang and Turner 2015[5]; Dunn et al. 2010[8])	Prescription opioids (Turner and Liang: 206,869 patients), MED range 0 to >100 mg/day; (Dunn: 9,940 patients), mean MED 13.3 mg/day)	Liang and Turner: The strongest associations with drug overdose were observed for ≥100 mg daily opioid dose regardless of total dose or 50 to 99 mg daily dose combined with a high total dose (>1,830 mg). Dunn: Overdose risk increased nine-fold for high dose opioids (≥100 mg/day) vs. the lowest opioid doses.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Opioid-related death	1 case-cohort study (Bohnert et al. 2011[12]) and 1 retrospective	Prescription opioids (Kaplovitch: 32,449 patients), MED mean and	Kaplovitch: Patients who escalated to high dose opioid therapy (>200 mg/day) were nearly 24 times as likely to die	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
	cohort study (Kaplovitch et al. 2015)[3]	range not reported; (Bohnert: 155,434 patients), MED range 0 to >100 mg/day)	as those who did not escalate (3.1% vs. 0.1%, respectively). Bohnert: Risk of overdose death was significantly increased with increasing maximum prescribed daily opioid dose (HR=7.18; 95% CI: 4.85–10.65 for ≥100 mg/d vs. 1-20 mg/d)					
Opioid Duration								
Opioid dependence/ OUD	1 retrospective cohort study (Edlund et al. 2014[6] and 1 cross-sectional cohort study (Boscarino et al. 2010[11])	Prescription opioids (Edlund: 568,640 patients), MED range 0 to >120 mg/day; (Boscarino: (705 patients) MED not reported)	Edlund: Opioid prescription was associated with significantly more OUD, and the effect varied by average daily dose and days' supply. Low dose, acute (OR=3.03; 95% CI: 2.32, 3.95), low dose, chronic (OR=14.92; 95% CI: 10.38, 21.46), medium dose, acute (OR=2.80; 95% CI: 2.12, 3.71), medium dose, chronic (OR=28.69; 95% CI: 20.02, 41.13), high dose, acute (OR=3.10; 95% CI: 1.67, 5.77), high dose, chronic (OR=122.45; 95% CI: 72.79, 205.99). Boscarino: Life-time opioid dependence was associated with higher numbers of opioid orders (OR=1.75, p=0.009), while opioid orders were not a significant factor in the final model for current opioid dependence.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Any aberrant result (from UDT)	1 retrospective cohort study (Turner et al. 2014)[7]	Prescription opioids (3,809 patients); MED range <40 mg/day to >120 mg/day (67.4% of patients received <40 mg/day)	Days' supply of opioids was not significantly associated with any aberrant result (OR=0.88; 95% CI: 0.75 to 1.04 for daily/near daily supply vs. less than daily supply)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Non-adherence (prescribed opioid non-detection from UDT)			Prescribed opioid non-detection was slightly less common among patients with daily/near-daily opioid supply vs. less-than-daily supply (OR=0.78; 95% CI: 0.63–0.96).					
Non-prescribed opioids (from UDT)			Non-prescribed opioids were weakly associated with excessive (vs. less than-daily) opioid supply (OR=1.59; 95% CI: 1.03–2.46).					
Opioid Prescription Refill Type (Regularly Scheduled, As Needed, or Both)								
Opioid-related overdose death	1 case-cohort study (Bohnert et al. 2011)[12]	Codeine, morphine, oxycodone, hydrocodone, oxymorphone and hydro-morphone (155,434 patients), MED range 0 to >100 mg/day	Opioid refill type was not significantly associated with overdose death in patients with CNCP, but a significant association was found among cancer patients (HR=2,75; 95% CI: 1.31–5.78 for as needed refill vs. regularly scheduled refill).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Age								
Opioid dependence/ OUD	5 cohort studies (3 retrospective and 2 cross-sectional) (Edlund 2014;[6] Huffman 2015;[2]	Prescription opioids (571,672 patients total), MED range 0 to >120 mg/day	Four out of 5 studies (including the largest study by Edlund) found a significant association between younger age and increased risk of opioid dependence or OUD (the studies used different age	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
	Banta-Green 2009;[9] Campbell 2015;[10] Boscarino 2010[11])		subgroups and cutoffs for their analyses). Edlund found the highest risk in the 18–30 years' subgroup (OR=10.51 vs. age 65+). The smallest study (Huffman) was the only study that did not find a significant association, and it may have lacked adequate statistical power.					
Any aberrant result (from UDT)	1 retrospective cohort study (Turner et al. 2014)[7]	Prescription opioids (3,809 patients); MED range <40 mg/day to >120 mg/day (67.4% of patients received <40 mg/day)	Any aberrant result was significantly less common among patients age 45–64 years (OR=0.77; 95% CI: 0.65–0.92) and 65+ years (OR=0.40; 95% CI: 0.32, 0.50) vs. patients aged 20–44 years.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Non-adherence (prescribed opioid non-detection from UDT)			Prescribed opioid non-detection was significantly less likely among patients aged 45+ versus 20–44 years.					
Non-prescribed opioids (from UDT)			Non-prescribed opioids were significantly less common among patients aged 45+ versus 20–44 years.					
Opioid-related respiratory/ CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	Opioid-related toxicity or overdose was weakly associated with age 55–64 (HR=1.9; 95% CI: 1.1–3.3) and 65+ years (HR=1.8; 95% CI: 1.1–3.2) vs. 18–34 years.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Overdose death	1 case-cohort study (Bohnert et al. 2011)[12]	Prescription opioids (155,434 pts), MED range 0 to >100 mg/day	Risk of overdose death was significantly decreased in age ≥50 categories, with lowest risk age ≥70 (HR=0.06; 95% CI: 0.02–0.18 vs. age 18–29 years)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Gender								
Opioid dependence/ OUD	4 retrospective cohort studies (Edlund 2014,[6] Huffman 2015,[2] Banta-Green 2009[9]) 1 prospective cohort (Jamison 2010[1]), and 1 cross-sectional cohort (Campbell 2015[10])	Prescription opioids (571,577 patients total), MED range 0 to >120 mg/day	Three out of 5 studies (including the largest study by Edlund) found a significant (but relatively weak) association between male gender and risk of opioid dependence/OUD. Of the 2 studies that did not, 1 was low quality and 1 was small enough that it may have lacked statistical power to detect a small association.	Serious limitations (-1)	Serious inconsistency (-1)	No serious indirectness	No serious imprecision	Low
Any aberrant result (from UDT)	1 retrospective cohort study (Turner et al. 2014)[7]	Prescription opioids (3,809 patients); MED range <40 mg/day to >120 mg/day (67.4% of patients received <40 mg/day)	Male gender was weakly associated with more aberrant UDT results (OR=1.24; 95% CI: 1.07-1.43)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Non-adherence (prescribed opioid non-detection from UDT)			Male gender was not significantly associated with prescribed opioid non-detection (OR=1.16; 95% CI: 0.9–1.40)					
Non-prescribed opioid			Male gender was not significantly associated with non-prescribed opioid detection (OR=1.03; 95% CI: 0.77–1.38)					
Overdose death	1 retrospective cohort study (Kaplovitch et al. 2015)[3]	Prescription opioids (32,449 patients), MED mean and range not reported	Men were twice as likely to experience an opioid-related death (adjusted HR=2.04; 95% CI: 1.18 to 3.53) compared to women.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Pain Interference or Impairment								
Opioid dependence	2 cross-sectional cohort studies (Campbell et al. 2015;[10] Boscarino et al. 2010[11])	Prescription opioids: (Campbell: 1,424 patients); median MED 75 (95% CI: 36–145) mg/day (Boscarino: 705 patients) MED not reported	Campbell: Pain interference was significantly associated with 12-month opioid dependence in univariate but not in multivariate analyses (Adj RR=1.05, 95% CI: 0.91–1.21). Pain severity was not associated with dependence in any analysis. Boscarino: Current pain impairment was weakly associated with lifetime opioid dependence (OR=1.94; p=0.01), but not current opioid dependence in multivariate analyses.	Very serious limitations (-2)	Serious inconsistency (-1)	No serious indirectness	No serious imprecision	Very Low
Race								
Any aberrant result (from UDT)	1 retrospective cohort study (Turner et al. 2014)[7]	Prescription opioids (3,809 patients); MED range <40 mg/day to >120 mg/day (67.4% of patients received <40 mg/day)	Race was not significantly associated with any aberrant result (OR=1.13; 95% CI: 0.81–1.56)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Non-adherence (prescribed opioid non-detection)			Race was not significantly associated with prescribed opioid non-detection (OR=1.14; 95% CI: 0.76–1.72)					
Non-prescribed opioid (from UDT)			Non-prescribed opioids were significantly more common among African-Americans than whites (OR=2.07; 95% CI: 1.16–3.69).					
Opioid-related respiratory/ CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	Opioid-related toxicity or overdose was weakly associated with being non-Hispanic white (vs. non-Hispanic black) (OR=1.8; 95% CI: 1.3–2.4)	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Overdose death	1 case-cohort study (Bohnert et al. 2011)[12]	Prescription opioids (155,434 patients), MED range 0 to >100 mg/day	Risk of overdose death was significantly decreased in black patients vs. white patients (HR=0.37; 95% CI: 0.24–0.59)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Marital Status								
Opioid dependence	1 cross-sectional cohort study (Campbell et al. 2015)[10]	Prescription opioids (1,424 patients); median MED 75 (95% CI: 36-145) mg/day	Marital status was not significantly associated with opioid dependence.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Opioid-related respiratory/ CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	Opioid-related toxicity or overdose was significantly associated with being widowed (OR=2.0; 95% CI: 1.4–3.0) and weakly associated with being never married (OR=1.4; 95% CI: 1.0–1.8) vs. married.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Employment Status								
Opioid dependence	1 cross-sectional cohort study (Campbell et al. 2015)[10]	Prescription opioids (1,424 patients); median MED 75 (95% CI: 36-145) mg/day	Unemployment was not significantly associated with opioid dependence in multivariate analyses (OR=1.31; 95% CI: 0.73–2.33).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (95% CI includes the possibility of a weak association)	Very Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Health Care Utilization								
Opioid-related respiratory/ CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	Days of hospitalization (≥1 vs. none) was significantly associated with opioid-related toxicity or overdose (OR=2.9; 95% CI: 2.3–3.6)	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low

[a] Methodological Quality takes into account the overall risk of bias rating of all the studies included in the evidence base;

[b] Inconsistency of results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed);

[c] Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population; and

[d] Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.

CI: confidence interval; CNCP: chronic non-cancer pain; CNS: central nervous system; COT: chronic opioid therapy; HR: hazard ratio; MED: morphine equivalent dose; OUD: opioid use disorder; OR: odds ratio; RR: relative risk; SD: standard deviation; TOA: therapeutic opioid addiction; UDT: urine drug test

Appendix A. Evidence Tables

Table 2. Individual Studies

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Reference: Campbell et al. 2015[10] **Country:** Australia **Study Design:** Cross-sectional cohort study **Purpose:** 1) Describe levels of current pharmaceutical opioid consumption, and the correlates of different levels of consumption; 2) Examine the prevalence of lifetime dependence and past year dependence as per ICD-10 criteria; and 3) Examine the correlates of the criteria met for pharmaceutical opioid dependence. **Quality Rating:** Poor Patients eligible but not participating were not compared with those who participated, so generalizability is unclear. Patients who did not provide OME data had more comorbidities than patients who provided OME data. All variables and outcomes were measured at the same time, so causality could not be determined. Study did not control for all relevant comorbidities, but did use multivariate analyses to adjust for several relevant variables.	**Number of Patients:** 1,424 **Diagnosis:** CNCP **Age (Years):** Median 58 years **Gender:** 55% female **Inclusion Criteria:** 18 years of age or older; fluent in English; mentally and physically able to complete telephone and self-complete interviews; without obvious cognitive impairment; living with CNCP; prescribed an opioid such as morphine, oxycodone, or fentanyl; and having taken such opioids for CNCP for more than 6 weeks. **Exclusion Criteria:** Those currently prescribed methadone or buprenorphine as opioid substitution therapy for heroin dependence or taking opioids for cancer pain were not eligible.	OME was determined through medication diaries (only 1,085 patients returned these). Opioid dependence was determined by interviews (1,424 patients completed the CIDI to determine ICD-10 dependence). OME groups were compared using multinomial logistic regression; relative risk ratios, and 95% CIs were used for proportions. The category of 21–90 mg/day OME was used as the reference group in the multinomial regressions, as this range represented usual therapeutic doses and the largest group in the sample. Two groups were defined according to whether or not they met ICD-10 criteria for pharmaceutical opioid dependence in the past year. Univariate logistic regression models were conducted to compare these groups. Relative risk and Hedges g are reported with 95% CI; a multivariate model was also conducted to determine the independence of associations of variables significant in bivariate analyses; these factors include age, gender, employment status, median number of pain conditions, pain interference score, PSEQ score, nonadherence, substance use (4 categories), depression, generalized anxiety disorder, and PTSD. Adjusted RR and 95% CI are reported. **Follow-up:** One year	**Opioid Dependence Risk Factors:** In the multivariate analyses, patients with past year pharmaceutical opioid dependence were: 1) younger (Adj RR 0.97; 95% CI: 0.95–0.99); 2) more likely to engage in aberrant behaviors (nonadherence Adj RR 2.47; 95% CI: 1.44–4.24); and 3) more likely to meet criteria for ICD-10 lifetime benzodiazepine dependence (Adj RR 3.22; 95% CI: 1.40–7.41). The authors ran a post hoc multivariate analysis including OME which resulted in: 1) age (RR 0.96; 95% CI: 0.93–0.99); 2) aberrant behaviors (RR 2.49; 95% CI: 1.18–5.24); and 3) ICD-10 lifetime benzodiazepine dependence (RR 4.31; 95%CI 1.55–12.63) remaining significant. Other substance abuse (smoking, alcohol, illicit drugs), mental health conditions (depression, anxiety, PTSD) and gender were not significantly associated with pharmaceutical opioid dependence in the multivariate analyses. In univariate analyses, OME ≥200 mg/day was significantly associated with pharmaceutical opioid dependence (lifetime and past 12 months), past 3 month tampering, illicit drug use, increased pain scores, and moderate-severe depression.

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Reference: Huffman et al. 2015[2] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To examine the associations of non-opioid SUDs, opioid dosage, and TOA in a population of patients thought to be representative of those at highest risk. **Quality Rating:** Fair Several relevant confounders were not adjusted for in the logistic regression; included patients did not differ significantly from excluded patients in demographics or history of SUD.	**Number of Patients:** 199 **Diagnosis:** Chronic non-cancer pain **Age (Years):** Mean 46.5 (±13.6) years **Gender:** 60.8% female **Inclusion Criteria:** Cases were included in the study if patients 1) were undergoing long-term opioid therapy at the time of admission or 2) had been weaned from opioids as part of chemical dependency treatment (or by virtue of running out of opioids) directly before admission. **Exclusion Criteria:** Patients were excluded if 1) they had a history of nonmedicinal opioid use that preceded the introduction of therapeutic opioids; 2) they had abused therapeutic opioids but did not meet full criteria for TOA; or 3) the diagnosis of TOA could not be excluded or made conclusively.	**Treatment:** All patients had undergone long-term opioid therapy before starting the study. The study treatment was a chronic pain rehabilitation program (5 days/week, 8 hrs/day for 3 to 4 weeks) that included weaning of opioids and other addictive medications, individual and group psychotherapy, physical therapy, occupational therapy, substance use education and monthly aftercare. A binary logistic regression, including gender and age as controls, was used to determine whether a lifetime history of a non-opioid substance use disorder or morphine equivalence dosage at time of admission predicted increased odds of having TOA. **Follow-up:** 3 to 4 weeks	**Risk Factors for TOA:** The final model found (after adjustment for age and gender): 1) lifetime history of an SUD was associated with 28 times increased odds of TOA (OR=28.5; 95% CI: 10.86, 75.27); and 2) opioid dose was associated with TOA. Each 10-mg increase of oral morphine was associated with a 12% increase in odds of TOA (OR=1.12; 95% CI: 1.05, 1.18). Each 50-mg increase was associated with a 73% increase in odds of TOA (OR=1.73; 95% CI: 1.29, 2.32). Each 100-mg increase was associated with 3-fold increase in odds of TOA (OR=3.00; 95% CI: 1.67, 5.41) after adjustment for age and gender. Gender and age were not significantly associated with TOA.
Reference: Kaplovitch et al. 2015[3] **Country:** Canada **Study Design:** Retrospective cohort study **Purpose:** To formally explore the relationship between sex, dose escalation and death due to overdose in a large cohort of patients receiving COT for non-cancer pain. **Quality Rating:** Fair Participation was high and attrition was low. Multivariate analysis adjusted for several potential confounding factors, although it did not adjust for	**Number of Patients:** 32,449 **Diagnosis:** Non-cancer pain and receiving COT **Age (Years):** Median 47 years (men), 44 years (women) **Gender:** 58% women **Inclusion Criteria:** Men and women who began treatment with an opioid, based upon prescriptions for oral codeine, morphine, oxycodone, hydromorphone or transdermal fentanyl. **Exclusion Criteria:** Patients with any other opioid prescription in the preceding year. Prescriptions for hydrocodone and methadone were excluded. Individuals with any	The authors used Cox proportional hazards regression to estimate the risks of dose escalation (to a dose >200 mg/day) and opioid-related mortality for men relative to women, after adjusting for all variables with a standardized difference greater or equal to 0.10, including age, documented alcohol-related disorder in the preceding 5 years, number of distinct non-opioid medications prescribed in the past 6 months and use of serotonergic antidepressants. They also adjusted for receipt of benzodiazepines, antipsychotic drugs and other psychotropic drugs or central nervous system (CNS) depressants in the preceding 180 days, as well as comorbidity defined using the Charlson comorbidity index.	**Risk Factors for Dose Escalation and Overdose Death**. 1) Gender: After multivariable adjustment, men were almost 50% more likely to escalate to high-dose opioids (adjusted HR=1.44; 95% CI, 1.21 to 1.70) and twice as likely to experience an opioid-related death (adjusted HR=2.04; 95% CI: 1.18 to 3.53) compared to women. 2) Dose escalation: Patients who escalated to high dose opioid therapy were nearly 24 times as likely to die as those who did not escalate (3.1% vs. 0.1%, respectively).

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
specific medical or mental health diagnoses. Adherence rates and illicit drug use could not be determined.	evidence of cancer prior to cohort entry, as well as patients with any physician claim or inpatient hospitalization for palliative care services in the 180 days preceding cohort entry were also excluded.	**Follow-up:** Patients were followed from their first opioid prescription until discontinuation of opioid treatment (defined as an interval of more than 120 days between successive prescriptions), death from any cause, or the end of study period (December 31, 2010), whichever occurred first. The maximum duration of publically-funded prescriptions in Ontario is 100 days.	
Reference: Turner and Liang 2015;[4] Liang and Turner 2015[5] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To examine interactions of filled prescriptions for opioids, benzodiazepines, antidepressants, and zolpidem with mental health disorders in regard to drug overdose. **Quality Rating:** Fair Good participation and low attrition, multivariate analysis controlled for most potential confounders. Limitations were use of coded diagnoses with limited sensitivity for mental health disorders; adherence to prescriptions could not be determined; some overdoses may have been due to illicit drug use.	**Number of Patients:** 206,869 **Diagnosis:** Non-cancer pain **Age (Years):** Mean 44.1 (±12) years **Gender:** 57% female **Inclusion Criteria:** The study cohort included persons aged 18 to 64 years with non-cancer pain who filled at least two Schedule II or III prescriptions for non-injectable opioid analgesics from January 2009 through July 2012. Eligible subjects were continuously enrolled at least 12months in the Aetna plan and had claims for service utilization at least 6 months before the first drug overdose event. **Exclusion Criteria:** The most frequent exclusions were due to incomplete opioid prescription data, missing diagnostic data, or a non-basal cell cancer diagnosis.	All patients received non-injectable opioid analgesics. The study outcome was drug overdose diagnosed from an inpatient or outpatient clinical encounter following the first filled opioid prescription. For each subject, this time-varying outcome was measured in each 6-month interval after the first filled opioid prescription until last enrollment or end of the study time frame. Using repeated-measures logistic regression with the generalized estimating equations method under an unstructured correlation matrix, the authors examined the effects of daily opioid dose and duration of filled prescriptions for psychoactive drugs on the odds of overdose, adjusting for time-fixed covariates (i.e., age, sex, and region) as well as time-varying covariates (i.e., chronic pain conditions, mental health, and substance use disorders). Clinical judgment guided a backward model selection procedure. The authors started with a full model including demographics, clinical conditions, substance use disorders (i.e., drug or alcohol), and medications, as well as all possible interactions of daily opioid dose with each of the three psychoactive drug groups (i.e., benzodiazepines, antidepressants, and zolpidem), and interactions of each of these drugs with mental health conditions (i.e., anxiety/PTSD, depression, and psychotic disorder). The final model included clinically	**Risk Factors for Drug Overdose:** In the fully adjusted model, the following significant interactions were observed: 1) opioid therapy with depression (chi(4)=36.53, p<0.001); 2) antidepressant therapy with depression (chi(3)=20.20, p<0.001); 3) benzodiazepine therapy with anxiety/PTSD (chi(3)=10.36, p=0.016) and 4) zolpidem therapy with anxiety/PTSD diagnosis (chi(3)=8.79, p=0.03). Opioid dose and depression: The adjusted odds of overdose were significantly higher for persons with depression regardless of opioid dose (all p<0.001). The AOR of drug overdose were 7.06 (95 % CI: 5.30 to 9.42) for the combined effect of depression and very high opioid dose (≥100 mg) vs. no depression or opioid use. An increasing opioid dose monotonically increased the likelihood of drug overdose (chi2(4)=24.20, p<0.001) with AOR 1.78, (95% CI: 1.39 to 2.29) for a very high opioid dose vs. no opioids. Opioid dose in persons without depression: Drug overdose was associated with increasing opioid dose (chi2(4)=161.4, p<0.001), but the risk rose gradually with all but a very high daily dose (AOR=4.34; 95 % CI: 3.37 to 5.57) vs. no opioids. Overall opioid dose: The strongest associations with drug overdose were observed for ≥100 mg daily dose regardless of total dose or 50 to 99 mg

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		important and/or statistically significant factors. **Follow-up:** 3.5 years	daily dose combined with a high total dose (>1,830 mg). Longer-term antidepressants (91–180 days) were protective for persons with depression, with 20% lower AORs for overdose vs. short-term (1–30 days) or none. For persons without depression, the AORs of overdose were increased for antidepressant use, but greatest (AOR=1.98) for short-term use versus none. Benzodiazepine therapy: The AORs of overdose increased with duration of benzodiazepine among all subjects, with >2.5-fold higher AORs for 91–180 days vs. none.
Reference: Edlund et al. 2014[6] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To investigate the association between exposure to prescription opioids and incident opioid use disorders (OUDs) among individuals with a new episode of a chronic non-cancer pain (CNCP) condition. **Quality Rating:** Fair High participation, low attrition, multivariable analysis adjusted for several (but not all) potential confounders	**Number of Patients:** 568,640 **Diagnosis:** CNCP **Age (Years):** ≥18 years, mean and range not reported **Gender:** 58.3% female **Inclusion Criteria:** The HealthCore dataset included all individuals aged 18 years or older with a new episode of a CNCP condition. Data was from years 2000 to 2005. The following criteria were used to identify new episodes of a CNCP condition: 1) Two or more claims containing primary or secondary diagnoses of the same type of CNCP (back pain, neck pain, headache, arthritis, HIV) that occurred at least 1 month apart but were not separated by more than 1 year; 2) No CNCP diagnoses of the same type in the 6 months prior to the first qualifying diagnosis. Individuals who already had a CNCP condition (e.g., back pain), were eligible for the analytical sample if they had a new episode of a different CNCP condition (e.g., headache). Eligible individuals were required to have 12 months of continuous eligibility prior to and 18	The outcome of interest was any diagnosis of an OUD (opioid abuse or dependence) occurring in the 18-month period after the index date. The outcome was binary and derived from ICD-9-CM codes (304.00, 305.50). Opioid daily doses were divided into 4 categories: none, low (1-36 mg), medium (36–120 mg) and high (>120 mg). Opioid days' supply was divided into 3 categories: none, acute (1–90 days), and chronic (>90 days). The authors regressed their measure of an OUD on the independent variables in both unadjusted and adjusted logistic regression. Covariates used in the adjusted analyses include opioid dose and days' supply, age in years, gender, number of types of tracer pains in the pre-index period, number of non-tracer pain categories, number of non-substance mental health disorder types, pre-index substance abuse/dependence diagnoses, and Charlson score. **Follow-up:** 18 months	**Opioid Dose and Duration:** In a multiple logistic regression, those prescribed opioids had significantly higher OUD rates compared to those not prescribed opioids, and the effect varied by average daily dose and days' supply: 1) low dose, acute (HR=3.03; 95% CI: 2.32, 3.95, p<0.001); 2) low dose, chronic (OR=14.92; 95% CI: 10.38, 21.46, p<0.001); 3) medium dose, acute (HR=2.80; 95% CI: 2.12, 3.71, p<0.001); 4) medium dose, chronic (HR=28.69; 95% CI: 20.02, 41.13, p<0.001); 5) high dose, acute (HR=3.10; 95% CI: 1.67, 5.77, p<0.001); and 6) high dose, chronic (HR=122.45; 95% CI: 72.79, 205.99, p<0.001). **Gender and Age:** 1) Men had higher rates of OUDs (OR=2.27; 95% CI: 1.85, 2.78, p<0.001), and 2) younger individuals had higher rates than older individuals. For example, the youngest group (ages 18 to 30) had an OR of 10.51 (95% CI: 5.47, 20.20, p<0.001), compared to the reference group (age 65+).

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	months of continuous eligibility after the index date. **Exclusion Criteria:** Individuals with OUD diagnoses and/or any prescription opioid use in the 6 months prior to the index date, individuals with a cancer diagnosis at any time in the 12 months before or after 18 months after the index date (other than non-melanoma skin cancer), residents of nursing homes, and those receiving hospice benefits were excluded.		**Pre-index Mental Health Disorders**: Individuals with pre-index mental health disorders had higher rates of OUDs (HR=3.12; 95% CI: 2.41, 4.04, p<0.001 for those with 1 mental health disorder type vs those with no mental health disorder, and OR=5.71; (95% CI: 3.83, 8.52, p<0.001) for those with 2 mental health disorder types vs. those with none. **Pre-index Substance Use Disorders:** 1) Individuals with a pre-index alcohol use disorder had a higher likelihood of a post-index OUD (adjusted HR=3.22; 95% CI: 1.79, 5.80, p<0.001) compared to those with no pre-index alcohol use disorder. 2) patients with pre-index non-opioid drug abuse disorders had higher rates of OUDs (OR=8.26; 95% CI: 4.74, 14.39, p<0.001) than those without pre-index non-opioid drug abuse disorders.
Reference: Turner et al. 2014[7] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To identify primary care COT patient and opioid regimen characteristics associated with aberrant UDT results. **Quality Rating:** Fair High participation from large primary care population, low attrition, multivariable analysis controlled for most (but not all) relevant potential confounders. Since most patients were on low-moderate doses of short-acting opioids, findings may not be generalizable to other settings with a higher	**Number of Patients:** 3,809 patients with 5,420 UDTs **Diagnosis:** CNCP **Age (Years):** ≥20 years, mean and range not reported **Gender:** 60.6% female **Inclusion Criteria:** All pain management UDTs performed January 2011–December 2012 for patients aged ≥20 years. UDT, pharmacy, and patient data was obtained from Group Health (GH) databases. The authors included only UDTs for patients on COT, defined by GH as ≥70 days' opioid supply in the prior 90 days. **Exclusion Criteria:** To limit the sample to UDTs for CNCP patients, we excluded those of patients who, in the one-year period prior to the UDT, had had hospice care, opioid prescriptions from oncologists, or	The GH pain management UDT includes a screening immunoassay and liquid chromatography-tandem mass spectrometry (LC-MS/MS) confirmatory test. The authors conducted descriptive analyses, then logistic regression analyses predicting dilute samples and the following LC-MS/MS UDT results (excluding dilute samples): (1) any aberrancy; (2) prescribed opioid non-detection (defined as negative for all opioids prescribed for prior 90 days); (3) THC but no illicit drug; (4) non-prescribed opioid; (5) illicit drug; and (6) non-prescribed benzodiazepine. Potential predictors included age, gender race, ethnicity, mental health diagnosis, alcohol used disorder, substance use disorder, current smoker, opioid daily MED, days' supply, and opioid type (short or long-acting). All predictors were entered in a multivariable model for each outcome that had sufficient counts for reliable results.	**Any Aberrant Result:** In multivariable analyses, adjusted odds ratios (AOR) and 95% CI for any aberrant result were higher for 1) males (HR=1.24 [1.07–1.43]), 2) patients with prior SUD diagnoses (HR=1.42 [1.17–1.72]), and 3) current smokers vs. non-smokers (1.50 [1.30–1.73]). They were lower for: 1) patients aged 45–64 (HR=0.77 [0.65, 0.92]) and 65+ (HR=0.40 [0.32, 0.50]) vs. patients aged 20–44, 2) those on 40 to <120 mg daily MED (HR=0.78 [0.65, 0.95]) vs. <40 mg MED, and 3) for patients on long-acting opioids only (HR=0.72 [0.55, 0.95]) or long-acting plus short-acting opioids (HR=0.67 [0.54, 0.83]) vs. short-acting opioids only. **Prescribed Opioid Non-detection** was more likely among patients with prior SUD diagnoses (HR=1.70; 95 % CI: 1.31, 2.20).

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proportion of substance abuse and higher dose opioid prescriptions.	more than one visit for cancer other than non-melanoma skin cancer. To ensure data availability, we excluded UDTs for patients not continuously enrolled at GH for the previous year.	**Follow-up:** Patient visit diagnoses were identified within 2 years prior to the index UDT.	It was less likely among: 1) patients aged 45+ versus 20–44, 2) on moderate (HR=0.52 [0.39, 0.70]) or high (HR=0.22 [0.11, 0.43]) doses vs. low doses, 3) with daily/near-daily opioid supply vs. less-than-daily supply (0.78 [0.63, 0.96]), and 4) on long-acting opioids (vs. short-acting opioids only). **Non-prescribed Opioids** were more common among: 1) African-Americans than whites (HR=2.07 [1.16, 3.69]) and 2) among patients with excessive (vs. less than-daily) opioid supply (1.59 [1.03, 2.46]), and less common among patients aged 45+ vs. 20–44.
Reference: Zedler et al. 2014[13] **Country:** USA **Study Design:** Retrospective nested case-control study **Purpose:** To examine factors associated with a diagnosis of serious opioid-related respiratory/CNS depression or overdose among VHA patients who were dispensed an opioid by VHA. **Quality Rating:** Poor Study did not report percent patients with acute or chronic pain or percent of patients with short-term opioid therapy vs. COT.	**Number of Patients:** 8,987 veterans **Diagnosis:** Pain diagnoses were not reported **Age (Years):** Median 62 years **Gender:** 92.1% male **Inclusion Criteria:** The study used VHA Medical SAS datasets from October 1, 2010 through September 30, 2012. "Cases" were defined as 1) patients who were dispensed at least one opioid prescription by VHA, identified by national drug code; and 2) had a claim for a serious opioid-related toxicity or overdose event based on ICD-9-CM codes and CPT codes. All patients were required to have non-missing age, sex, and race values in addition to continuous medical and pharmacy benefits in the 6 months before the index date (the "baseline period"). For each case, 10 control patients were randomly selected and assigned from those who 1) were dispensed an	The study included 817 cases and 8,170 controls. A serious opioid-related toxicity or overdose event was defined as follows: 1) a listed CNS or respiratory adverse effect code in addition to a listed poisoning event or external cause code occurring within ±1 day of the adverse effect; or 2) use of mechanical ventilation or critical care in addition to a listed poisoning event or external cause code occurring within ±1 day of the critical respiratory support. The first identified occurrence of opioid-related overdose or life-threatening respiratory/CNS depression ("index event") during the study period served as the "index date" for cases. Multivariable analysis was performed using conditional logistic regression to examine factors potentially associated with the index event of serious opioid-related toxicity or overdose. The covariates included in the regression model were age, sex, race/ethnicity, marital status, US Census region, comorbidities, prescription opioid characteristics, the maximum prescribed daily MED, selected non-care resource utilization.	**Risk Factors for Serious Opioid-related Respiratory/CNS Depression or Overdose:** The multivariable analysis identified the following variables as having the strongest associations with the outcome: 1) History of opioid dependence (HR=3.9; 95% CI: 2.6–5.8), 2) Max prescribed daily opioid MED ≥100 mg/day (HR=4.1; 95% CI: 2.6–6.5), 3) ≥1 day of hospitalization during prior 6 months (HR=2.9; 95% CI: 2.3–3.6) Other factors that showed smaller significant associations (and smaller ORs) with the outcome were: 1) Age groups 55–64 and 65+ years (vs.18–34 years), 2) Race (non-Hispanic white vs. non-Hispanic black, 3) Marital status widowed or never married, 4) Geographic region West, 5) COPD, 6) Use of warfarin,

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	opioid by VHA during the study period; 2) did not experience serious opioid-related toxicity or overdose as defined in the study; and 3) had complete data for age, sex, and race. **Exclusion Criteria:** Not reported	opioid prescription medications, and baseline health **Follow-up:** Baseline period covered 6 months prior to the index event. For cases, the follow-up period was calculated as the number of days after the end of the event until death, disenrollment, or the end of the study period. Matched controls were given the same index-date and follow-up.	7) Renal disease, 8) Skin ulcers, 9) Moderate or severe liver disease, 10) Metastatic solid tumor, 11) Substance abuse and nonopioid substance dependence 12) Pancreatitis, 13) Sleep apnea, 14) BPD, 15) Traumatic injury, 16) Oxycodone and hydromorphone, 17) Extended-release/long-acting opioids, 18) Max opioid MED 20-100 mg/daily 19) Benzodiazepines, antidepressants, and antipsychotics
Reference: Bohnert et al. 2011[12] **Country:** USA **Study Design:** Case-cohort study **Purpose:** To examine the association of maximum prescribed daily opioid dose and dosing schedule ("as needed," regularly scheduled, or both) with risk of opioid overdose death among patients with cancer, chronic pain, acute pain, and substance use disorders. **Quality Rating:** Fair Appropriate case ascertainment (although some deaths could have been suicides misclassified as accidental overdoses), nonbiased selection of cases	**Number of Patients:** 155,434 **Diagnosis:** CNCP or cancer-related pain **Age (Years):** ≥18 years (mean and range not reported) **Gender:** 93.3% male **Inclusion Criteria:** The authors included two 5% random samples of VHA patients treated with opioids (one each for fiscal year [FY] 2004 and FY2005), as well as all FY2004 and FY2005 VHA patients who died of an opioid overdose before the end of FY2008 ("cases"). **Exclusion Criteria:** Individuals with indicators of palliative care consultations or hospice care in their VHA medical records were excluded.	The prescribed opioids included codeine, morphine, oxycodone, hydrocodone, oxymorphone and hydromorphone. Methadone was not included in the analysis because of its unique indications, duration of action, and inconsistent morphine equivalency. The authors developed Cox proportional hazards models to examine the relationship of opioid prescribing and risk of opioid overdose death adjusting for demographic and clinical characteristics. Multivariable modeling was restricted to periods when individuals were prescribed at least 1 opioid. Separate models were created for patients with CNCP (n=111,759), cancer pain (n=36,803), acute pain, and substance use disorders (these latter 2 were outside the scope of our analysis). Variables included in the models were opioid fill type, maximum prescribed daily dose, pain-related diagnoses, other diagnoses (SUD; psychiatric disorders;	**Cox Proportional Hazards Models of Risk of Death by Prescription Opioid Overdose:** **Chronic pain patients:** Risk of overdose death was significantly increased with: 1) higher max prescribed daily opioid dose (HR=7.18; 95% CI: 4.85–10.65 for ≥100 mg/d vs. 1–20 mg/d), 2) SUD diagnosis (HR=2.53; 95% CI: 1.99–3.22), and 3) diagnosis of other psychiatric disorders (HR=1.87; 95% CI: 1.48–2.38). Risk was significantly decreased for: 1) age ≥50 categories, with lowest risk age ≥70 (HR=0.06, 95% CI: 0.02–0.18 vs. age 18–29 years), 2) in black patients vs. white patients (HR=0.37; 95% CI: 0.24-0.59), and 3) diagnosis of COPD, CVD or sleep apnea (HR=0.63; 95% CI: 0.50–0.80).

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and controls, diagnostic procedures and measures applied equally to cases and controls, and all appropriate confounding variables were controlled for in multivariable analyses. Use of medical records may have resulted in under-detection of medical conditions.		COPD, CVD, and sleep apnea), gender, age, and race. **Follow-up:** mean length of follow-up not reported. For cases, observation time began on the date of the first opioid fill that occurred after the first medical visit within the study period to avoid potential immortal person-time. Similarly, for all non-cases, observation time began on the date of the first opioid fill that occurred after the first medical visit in the year for which the individuals were in the random sample. Observation time ended on the day of death or the end of FY2008, whichever came first.	**Cancer patients:** Risk of overdose death was significantly increased with: 1) higher max prescribed daily opioid dose (HR=11.99; 95% CI: 4.42–32.56), 2) opioid prescription refills as needed (HR=2.75; 95% CI: 1.32–5.78 vs. regularly scheduled refills), and 3) diagnosis of SUD (HR=3.08; 95% CI: 1.73–5.51). Risk was significantly decreased by age ≥60 years (HR=0.06; 95% CI: 0.01-0.64). Higher opioid dose had the same association with overdose death in additional separate subgroups of patients with acute pain and SUDs.
Reference: Boscarino et al. 2010[11] **Country:** USA **Study Design:** Cross-sectional study supplemented with retrospective database review **Purpose:** To assess the prevalence of and risk factors for opioid drug dependence among out-patients on long-term opioid therapy in a large health-care system. **Quality Rating:** Poor Low survey completion rate (33%), completers differed from non-completers in gender, marital status, smoking status, and general health. Case weights were developed to adjust for differences in participation by gender and clinic setting, but did not adjust for other differences. Diagnostic data were based on patient self-report. Multivariate	**Number of Patients:** 705 **Diagnosis:** Non-cancer pain **Age (Years):** ≥18 years, but mean and range not reported **Gender:** Not reported **Inclusion Criteria:** Patients were eligible for this study if they were 18+ years of age, received care from one of nine community practice clinics or from the three specialty clinics, including a pain management, orthopedics and a rheumatoid clinic, and were prescribed opioid medications 4+ times for non-malignant pain any time from June 30, 2006 to July 1, 2007. **Exclusion Criteria:** Of patients contacted by phone, 234 were determined to be ineligible for study, due to death, institutionalization, language barriers, illness, denial of opioid use or due to being in the last survey batch not contacted because the study quota was completed.	Patients who met inclusion criteria underwent structured diagnostic interviews that included: (i) a modified Composite International Diagnostic Interview (CIDI); (ii) assessment of depression, PTSD, general anxiety and psychological trauma using a diagnostic interview designed for this purpose; and (iii) questions relevant to severity of opioid dependence, tobacco dependence, and childhood neglect. Substance misuse and dependence were defined using DSM-IV criteria. Response bias was analyzed using EHR data to compare study respondents (n=705) to eligible non-respondents (n=1,434). These results led to development of weights to adjust for potential response bias. Logistic regressions were used to identify risk factors for opioid dependence. To identify useful models, only variables with bivariate p-values <0.10 were selected. In addition, only variables that remained significant at p<0.10 were retained in the final multivariate models. **Follow-up:** Outcomes were measured at time of interview, while some risk factor data came	**Model 1: Life-time Opioid Dependence:** Life-time opioid dependence was associated with: 1) age <65 (OR=2.80; p<0.001), 2) current pain impairment (OR=1.94; p=0.01), 3) history of opioid abuse (OR=3.95; p<0.001), 4) higher life-time opioid dependence severity (OR=3.00; p=0.003), 5) higher numbers of opioid orders (OR=1.75; p=0.009) and 6) history of antisocial personality disorder (OR=1.44; p=0.015). **Model 2: current opioid dependence** Current opioid dependence was associated with 1) age <65 (OR=2.33; p=0.001), 2) history of opioid abuse (OR=3.81; p<0.001), 3) higher life-time opioid dependence severity (OR=1.85; p=0.001), 4) history of major depression (OR=1.29; p=0.022) and 5) psychotropic medication use (OR=1.73; p=0.006).

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regressions adjusted for most (but not all) relevant potential confounders.		from medical records covering the past 3 years prior to the interview.	
Reference: Dunn et al. 2010[8] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To estimate rates of opioid overdose and their association with average prescribed daily opioid dose among patients receiving medically prescribed chronic opioid therapy. **Quality Rating:** Fair High participation but >80% attrition (partly due to the long follow-up period); multivariate analysis controlled for most relevant confounding factors	**Number of Patients:** 9,940 **Diagnosis:** CNCP **Age (Years):** mean 54 (range 18 to 99) years **Gender:** 59.6% female **Inclusion Criteria:** (i) adults aged 18 or over initiating a new episode of opioid use (no opioid prescriptions filled in the previous 6 months) between 1997 and 2005 (inclusive), (ii) 3 or more prescriptions for opioid analgesics in the first 90 days of the episode, and (iii) a diagnosis of a non-cancer pain problem from the prescribing physician in the two weeks prior to the initial opioid prescription. **Exclusion Criteria:** (i) individuals with a cancer diagnosis (except non-melanoma skin cancer) in the Cancer Surveillance and End Results Registry up to the end of 2006, (ii) two or more cancer diagnoses (excluding non-melanoma skin cancer) from visit or hospital data between the episode start date and the date of censoring, (iii) individuals not enrolled for at least 270 days in the one-year period prior to study cohort entry.	Average daily opioid dose over the previous 90 days was determined from automated pharmacy data. Primary outcomes, non-fatal and fatal overdoses, were identified through diagnostic codes from inpatient and outpatient care and death certificates and confirmed by medical record review. A Cox proportional hazards model was used to estimate the risk of overdose across individuals as a function of their average daily opioid dose. Opioid dose was included as a time varying covariate, estimated for continuously updated 90-day exposure windows. Estimated hazard ratios for opioid dose were based on comparing the opioid dose for an individual who had an overdose (evaluated at the time of event), relative to the opioid dose for all other individuals at risk for overdose at the time of the event (i.e., at the same number of days since entering the study cohort). Whether each person had initiated (started or restarted) opioid use in the prior 90 days was included in the model as a time-varying covariate. Sedative hypnotic use was included as a time varying covariate, estimated for continuously updated 90-day exposure windows. Hazard ratios were also adjusted for the following covariates not treated as time-varying: age (included as a continuous variable), sex, tobacco use, depression diagnosis, substance abuse diagnosis, index pain diagnosis, and chronic disease comorbidity adjustors (included as continuous variables). **Follow-up:** Patients were followed for a mean of 42 months (range <1 to 119 months) from their initial 90-day exposure window.	**Risk Factors for Overdose:** In multivariate analyses, the risk of overdose increased with increasing opioid dosage level. For an opioid dose of ≥100 mg per day, the annual overdose rate was 1,791 per 100,000 person years, a nine-fold increase in overdose risk (HR=8.87; 95% CI: 3.99, 19.72) compared to those receiving the lowest doses (1–<20 mg/day). The finding was similar for serious overdose events (death or serious non-fatal event, HR=11.18; 95% CI: 4.80–26.03) Recent initiation of opioid use (starting or restarting) was not associated with either increased or reduced risk of opioid overdose (data not shown). Recent reception of sedative-hypnotic medications was also associated with increased risk of opioid overdose, but frequency of receiving sedative-hypnotic medications was not related to risk. Relative to persons not receiving any sedative-hypnotic medications in the 90 days prior to opioid overdose, the overdose HRs were as follows: HR=3.4 (1.6–7.2) for 1–22 days' supply; HR=0.9 (0.2–4.0) for 23–44 days' supply; HR=3.7 (1.6–8.9) for 45–71 days' supply; and HR=2.7 (1.2–6.0) for 72+ days' supply.

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Reference: Jamison et al. 2010[1] **Country:** USA **Study Design:** Prospective cohort study **Purpose:** To examine, among persons prescribed opioids for pain, gender differences in: 1) the rates and characteristics of problematic opioid use, 2) the profile of risk factors for potential opioid misuse, and 3) longitudinal predictive associations between risk factors and subsequent misuse behaviors. **Quality Rating:** Poor Patient response rate not reported, so response bias cannot be assessed. Attrition was high (25.8%) and missing patients were significantly younger than patients with complete follow-up. Patients were from specialty care rather than primary care, so the findings may not generalize to the primary care setting. There was no multivariate analysis to control for relevant potential confounders.	**Number of Patients:** 610 **Diagnosis:** CNCP **Age (Years):** Mean 50.4 (range 21–89) years **Gender:** 54.8% women **Inclusion Criteria:** CNCP patients were recruited from pain management centers in five states (Massachusetts, New Hampshire, Pennsylvania, Ohio, and Indiana) as part of a larger study. Patients prescribed opioids for their pain were informed about the study and invited to participate. **Exclusion Criteria:** Not reported	The authors utilized three modes of assessment to measure aberrant drug-related behavior (misuse or abuse), ranging from objective findings on urine toxicology assays, to quasi-objective physician ratings of aberrant drug-related behavior, to patient self-report during a structured interview. Baseline measures included SOAPP-R, BPI, and the Marlow-Crowne Social Desirability Scale. End-of-study measures included the PDUQ, POTQ (physician ratings), urine toxicology screens, and the ADBI. Relations among demographic data, interview items, and questionnaire data were analyzed using Pearson product moment correlations, and Chi-square and t-test analyses depending whether the variables were ordinal or numerical. A discriminant function analysis was run to determine which items among the questionnaire items and which outcome data were most useful in identifying gender differences among the subjects. Predictive analyses using the SOAPP-R items involved t-tests performed separately in men and women. **Follow-up:** 5 months	**Gender Differences on End-of-study Measures:** Variable / Male / Female / p PDUQ total: 7.83 (3.8) / 8.74 (4.48) / <0.05 POTQ total: 1.14 (1.82) / 0.82 (1.63) / <0.05 Abnormal Urine: 33.6% / 37.4% / NS ADBI: 31% / 36.7% / NS **Capability of individual SOAPP-R items to predict aberrant behavior at 5 months (measured by positive urine screen or POTQ score ≥2):** T-tests revealed that 1 SOAPP-R item was predictive only for women, while 6 items were only predictive for men. The item that was predictive for women referred specifically to the medication-specific behavior of counting pills, while the majority of items that were predictive for men appeared to be related to a history of drug and alcohol abuse (i.e., having close friends who abuse drugs or alcohol, a history of legal problems and treatment for drug and alcohol abuse).
Reference: Banta-Green et al. 2009[9] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To categorize types of patients who are prescribed opioids chronically in a large	**Number of Patients:** 704 **Diagnosis:** CNCP **Age (Years):** Range 21-79 years. Mean reported separately for different latent classes: Typical (mean 55.9 years); Addictive Behaviors (mean 52.24 years); Pain Dysfunction (mean 53.8 years)	A summary factor score was used for each of the seven factors of interest derived from confirmatory factor analyses. Based on items from DSM-IV opioid use and dependence and the PDUQ, opioid use behaviors were summarized with four factor scores representing the areas of (1) Addictive Behaviors, (2) Addiction Concerns, (3) Pain Treatment Problems and (4) Opioid	**Independent associations between automated and interview data and most likely patient class using multivariate multinomial stepwise regression.** Addictive Behaviors vs. Typical OR (p-value) Avg prescribed daily dose opioids (log10): **3.67*** (<0.001)

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
integrated group practice (primary care) and to explore whether automated health plan data and simple screening tools could potentially be used to identify these different patient types. **Quality Rating:** Fair Response rate 57% among eligible patients; non-respondents were significantly more likely to be younger, male, and have higher opioid dose than respondents, which indicates response bias. These variables were adjusted for in multivariate statistical analyses along with other relevant potential confounding variables.	**Gender:** Typical (65% female); Addictive Behaviors (49% female); Pain Dysfunction (55% female) **Inclusion Criteria:** Patients with chronic opioid use in the 12-month period one year prior to the time of the interview were included. **Exclusion Criteria:** Patients with cancer were excluded except for those with benign, non-melanoma skin cancers. Patients reporting no opioid use in the 90 days preceding the interview were excluded from these analyses.	Abuse/Dependence. Latent class analysis (LCA) determined a 3-class model to be most appropriate: Typical (n=580), Addictive Behaviors (n=82), and Pain Dysfunction (n=42). Multivariate multinomial regression was used to explore the associations between selected automated and interview variables with each of the classes identified with the LCA. Variables were included in the multinomial regression if: 1) prior research indicated the variable was significantly associated with any of the domains of interest, or 2) bi-variate, unadjusted statistics indicated the distribution of the variable differed significantly (univariate p-value <0.20 for the omnibus test) across patient types. Next, variables were included in a stepwise method of selection for the multivariate multinomial regression model. **Follow-up:** Medical and pharmacy records were utilized to identify diagnoses and prescription information within 3 years prior to the patient interviews.	Sedative potential problem **3.23*** (0.009) Age* **0.97*** (0.009) Male **1.85*** (0.021) Mood disorder visit (per year) 1.47 (0.168) Non-opioid drug problem diagnoses 1.12 (0.807) Alcohol potential problem 1.98 (0.117) <u>Pain dysfunction vs. Typical</u> Avg prescribed daily dose opioids (log10) **6.18*** (<0.001) Non-opioid drug problem diagnoses **2.75*** (0.044) *Younger age was associated with addictive behaviors. *Bolded ORs are statistically significant.

ADBI: aberrant drug behavior index; AOR: adjusted odds ratio; BPD: borderline personality disorder; BPI: brief pain inventory; CI: confidence interval; CIDI: composite international diagnostic interview; CNCP: chronic non-cancer pain; COPD: chronic obstructive pulmonary disease; COT: chronic opioid therapy; CSA: chronic short-acting; CVD: cardiovascular disease; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ED: emergency department; EHR: electronic health record; FY: fiscal year; GAD: generalized anxiety disorder; GH: group health; HR: hazard ratio; ICD: International Statistical Classification of Diseases and Related Health Problems; IPDE: International Personality Disorder Examination; KPCO: Kaiser Permanente Colorado; MED: morphine equivalent dose; MOS-SS SOBH: medical outcomes study sleep scale, awakening due to shortness of breath or headache; NA: negative affect; NS: not significant; OME: oral morphine equivalents; OUD: opioid use disorder; OR: odds ratio; PDUQ: prescription drug use questionnaire; POINT: pain and opioids in treatment; POTQ: prescription opioid therapy questionnaire; PSEQ: pain self-efficacy questionnaire; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; RR: relative risk; SOAPP-R: screener and opioid assessment for pain patients; SNRI: serotonin-norepinephrine reuptake inhibitor; SUD: substance use disorder; THC: tetrahydrocannabinol; TOA: therapeutic opioid addiction; UDT: urine drug test; VHA: Veterans Health Administration

Appendix B. References

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Appendix C. Excluded Studies

Table 3. Excluded Studies

Reference	Reason for Exclusion
Agarin et al. 2015[16]	Upon reviewing full text: Does not address a key question
Arteta et al. 2015[17]	Study used surrogate outcome (COMM risk score) to assess opioid misuse risk
Barry et al. 2011[18]	Study does not report % patients with chronic pain, and only a small % had opioid prescriptions
Becker et al. 2009[19]	No information on % patients taking opioids, only reports on overall prescription drug
Brady et al. 2016[20]	Not a systematic review or clinical trial of any design
Broekmans et al. 2010[21]	<80% of patients had opioid prescriptions
Chapman et al. 2015[22]	Systematic review with no relevant studies
Chou et al. 2009[23]	Already reviewed in 2010 VA-DOD COT guideline
Cicero et al. 2009[24]	Analysis inadequate to address the question
Cochran et al. 2014[25]	Does not report % patients with chronic pain
Darnall et al. 2012[26]	The few relevant studies in the review were already included in our report.
Dennis et al. 2015[27]	Upon reviewing full text: Does not address the key question
Dhingra et al. 2015[28]	Study does not distinguish acute from chronic pain
Edlund et al. 2010[29]	Retrospective study with no multivariate analyses
Fishbain et al. 2012[30]	Review contained no relevant references that met inclusion criteria
Green et al. 2011[31]	Condition is substance abuse, study does not report on pain diagnoses
Green et al. 2009[32]	<80% patients had chronic pain (55% had a "pain problem" which was not further defi
Han et al. 2013[33]	Does not report on an outcome of interest (refer to protocol)
Hansen et al. 2011[34]	<80% patients had opioid prescriptions
Heiwe et al. 2011[35]	Not a comparative trial
Hojsted et al. 2013[36]	Does not report on an outcome of interest (refer to protocol)
Jamison et al. 2013[37]	Does not report on an outcome of interest (refer to protocol)
Johnson et al. 2012[38]	Case-control with inappropriate control group
Jones and Moore 2013[39]	Uses risk score rather than specific variables (e.g., history of opioid misuse, depressi predictor of opioid misuse
Kobus et al. 2012[40]	Does not report on an outcome of interest (refer to protocol)
Langley et al. 2010[41]	All primary studies published prior to 2009
Lanier et al. 2012[42]	Less than 40% of control group with pain
Lewis et al. 2010[43]	Cross-sectional study with no multivariate analysis
Liebschutz et al. 2010[44]	Study does not separate opioid use from other prescription drug use
Madadi et al. 2013[45]	Study only reviews cases (opioid-related deaths) and has no controls
Makris et al. 2015[46]	Upon reviewing full text: Does not address a key question
Marino et al. 2013[47]	Study used surrogate outcome (COMM risk score) to assess opioid misuse risk
Minozzi et al 2012[48]	Upon reviewing full text: Does not address a key question
Morasco et al. 2013[49]	Study uses risk scores instead of specific variables to predict outcomes

Reference	Reason for Exclusion
Nielsen et al. 2015[50]	Upon reviewing full text: Does not address a key question
Oviedo-Joekes et al. 2015[51]	Condition is not chronic pain
Passik et al. 2011[52]	Retrospective study with no multivariate analyses
Paulozzi et al. 2012[53]	Condition is not chronic pain
Paulozzi et al. 2014[54]	Retrospective study with no multivariate analysis
Pilgrim et al. 2013[55]	Upon reviewing full text: Does not address a key question
Sekhon et al. 2013[56]	Retrospective study with no multivariate analysis
Skinner et al. 2012[57]	Cross-sectional study with no relevant outcomes
Starrels et al. 2011[58]	Does not report on an outcome of interest (refer to protocol)
Sullivan et al. 2010[59]	Surrogate outcome for opioid misuse, retrospective study with no multivariate analysi

Key Questions 3 and 4: What is the comparative effectiveness and safety of COT versus other treatment modalities? a.) What is the comparative effectiveness and safety of COT versus no opioid therapy or other treatment modalities for patients with a history of or current SUD?

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Key Questions 3 and 4: What is the comparative effectiveness and safety of COT versus other treatment modalities? a.) What is the comparative effectiveness and safety of COT versus no opioid therapy or other treatment modalities for patients with a history of or current SUD?

Summary of Evidence Base

Our searches identified 18 studies (1 systematic review,[1] 17 randomized controlled trials [RCTs][2-18]) that met criteria for this key question. We include information on both effectiveness and safety of 12 long-term studies (≥3 month follow up) evaluating buprenorphine transdermal delivery system (BTDS), fentanyl buccal tablets (FBT), hydrocodone extended release (ER), OROS hydromorphone hydrochloride, oxycodone ER, and tapentadol ER versus placebo.[1-12] Due to short-term follow-up (<3 month follow up) which did not meet inclusion criteria for effectiveness, information on safety is included for 6 studies.[13-18] Comparisons for these studies include BTDS versus placebo, controlled release (CR) oxycodone/CR naloxone versus placebo, and tramadol versus placebo and flupirtine, a centrally acting nonopioid analgesic.[15] We briefly summarize outcomes for all included studies below. Additional study information is provided in Table 2, Table 3-a, and Table 3-b.

Buprenorphine Transdermal Delivery System Versus Placebo (long-term studies)

- Efficacy: Significant findings were demonstrated in favor of buprenorphine transdermal delivery system (BTDS) over placebo for pain on the 11-point numerical rating scale (NRS-11) in patients with chronic low back pain (LBP) and osteoarthritis (2 RCTs, 740 patients;[11,12] Strength of evidence [SOE]: Moderate) Breivik et al. 2010[11] reported no benefit for BTDS over placebo in the primary endpoint of pain on the WOMAC OA pain subscale or secondary outcomes of stiffness, functional ability, and overall score on the WOMAC OA index (1 RCT, 199 patients;[11] SOE: Low). Significant findings favoring BTDS were reported for the secondary outcomes sleep disturbance (1 RCT, 541 patients;[12] SOE: Low) and patient global impression of change (1 RCT, 199 patients;[11] SOE: Low).
- Safety: Serious AEs occurred in 5% and 1.1% of patients treated with BTDS in 2 RCTs (738 patients;[11,12] SOE: Low). Serious AEs possibly or probably related to BTDS included vomiting and dehydration and abdominal pain, nausea, migraine, and constipation.[11] Serious AEs that occurred in another RCT, with no comment on relation to the study drug, were immediate-release oxycodone abuse, acute major depressive disorder, subarachnoid hemorrhage, motor vehicle accident, and acute renal failure and metastatic prostate cancer.[12] AEs caused 31% and 16% of patients treated with BTDS to drop out of the studies (2 RCTs, 738 patients;[11,12] SOE: Low). Common AEs (e.g., constipation, nausea, vomiting, dizziness) occurred at much higher rates with BTDS compared with placebo in 1 RCT,[11] while rates were more comparable between groups in another RCT[12] (SOE: Low).

Buprenorphine Transdermal Delivery System Versus Placebo (short-term study)

- Safety: No serious AEs were reported with BTDS. Significantly more AEs occurred in the BTDS group including nausea, vomiting, somnolence, dry mouth, and dizziness. More patients in the BTDS group dropped out due to AEs than in the placebo group (1 RCT, 78 patients;[16] SOE: Low).

Fentanyl Buccal Tablets Versus Placebo (long-term study)

- Efficacy: Significant findings were demonstrated in favor of FBT compared with placebo for both primary (sum of the pain intensity difference 60 minutes post-dose) and secondary outcomes (pain intensity and pain relief) in adults with non-cancer related pain (1 RCT, 79 patients;[10] Strength of evidence (SOE): Low).
- Safety: Application-site AEs (including erythema and swelling) and serious AEs (including pneumonia) occurred in 7% of patients. Nausea (15%) and dizziness (11%) were the most commonly reported AEs. Drug abuse occurred in 1 patient.

Hydrocodone Extended Release versus Placebo (long-term study)

- Efficacy: Mixed results were demonstrated for the primary efficacy outcome (change in average pain intensity [API]) in adults with osteoarthritis (OA) and low back pain (LBP) (2 RCTs, 594 patients;[4,5] SOE: Very low). Significant findings were demonstrated in favor of hydrocodone ER for 5 pain-related secondary outcomes while non-significant findings were demonstrated for 5 outcomes measuring function, symptom severity, pain, and quality of life (1 RCT reporting on each outcome; SOE: Low).
- Safety: Serious AEs (including acute pancreatitis) occurred in 6 patients. One study reported nausea and constipation in 13% of patients and diversion in 4 patients.[4]

OROS Hydromorphone Hydrochloride Versus Placebo (long-term study)

- Efficacy: Significant findings favoring OROS hydromorphone were demonstrated for primary (pain on NRS-11) and secondary outcomes (pain intensity, time to treatment failure, patient global assessment, and functional ability) in adults with chronic LBP (1 RCT, 266 patients;[9] SOE: Low). No significant findings for primary (pain on 10-point Brief Pain Inventory) or secondary outcomes (WOMAC OA scores, SF-36 pain scores, health-related quality of life) were reported in patients with OA of the hip or knee (1 RCT, 288 patients;[8] SOE: Low).
- Safety: Serious treatment-emergent AEs (TEAEs) were reported less frequently with OROS hydromorphone (1 RCT, 288 patients;[8] SOE: Low); however, serious AEs were reported more frequently with OROS hydromorphone in another study (1 RCT, 268 patients;[9] SOE: Low). Patients treated with OROS hydromorphone dropped out of studies due to AEs more frequently than patients treated with placebo (2 RCTs, 556 patients;[8,9] SOE: Low).

Controlled Release Oxycodone/Controlled Release Naloxone Versus Placebo (short-term study)

- Safety: Serious AEs occurred at the same rate (4.8%) in CR oxycodone/CR naloxone and placebo groups; the investigator determined none was related to the study drug. More patients dropped out due to AEs in the CR oxycodone/CR naloxone group (1 RCT, 83 patients;[18] SOE: Moderate).

Oxycodone Extended Release Versus Placebo (long-term studies)

- Efficacy: Significant findings were demonstrated in favor of oxycodone ER compared with placebo for pain-related primary (change in API) and secondary outcomes in adults with OA and LBP (2 RCTs, 801 patients;[6,7] SOE: Low). Results were mixed for quality of life (QOL) and function (SOE: Very low and Low).

- Safety: Serious AEs (including worsening erectile dysfunction and orthostatic hypotension) occurred in 14 patients. Gastrointestinal disorders occurred in over 24% of patients in both studies.

Tapentadol Extended Release Versus Placebo (long-term studies)

- Efficacy: Significant findings were demonstrated in favor of tapentadol ER compared with placebo for pain-related primary (change in API) and secondary outcomes in adults with knee OA, LBP, and diabetic peripheral neuropathy (DPN)(1 systematic review[1] and 2 RCTs,[2,3] 2,680 patients; SOE: Low). Results were mixed for 6 QOL-related outcomes (SOE: range Very low to Moderate).
- Safety: Serious AEs included chest pain (5 patients),[2,3] coronary artery disease (2 patients),[3] severe upper abdominal pain possibly related to study drug (1 patient)[2] and death due to myocardial ischemia doubtfully related to study drug (1 patient).[3] Nausea (21.1%) and vomiting (12.7%) occurred in over 12% of patients in one study.[3]

Tramadol Extended Release Versus Placebo (short-term studies)

- Safety: A single serious AE was reported, which was considered unrelated to study drug (1 RCT, TEAEs (1 RCT, 236 patients;[15] SOE: Low) and more patients in the tramadol ER group dropped out due to AEs (2 RCTs, 295 patients;[13,14] SOE: Low). Patients were more likely to experience nausea and dizziness (2 RCTs, 481 patients[14,15]), vomiting (1 RCT, 236 patients[15]), and headache (1 RCT, 245 patients[14]) with tramadol ER (SOE: Low for all AEs).

Tramadol Extended Release Versus Flupirtine (short-term study)

- Safety: No serious TEAEs were reported. Significantly more TEAEs were experienced in the tramadol ER group, and they presented significantly sooner than those in the flupirtine group. The drop-out rate due to TEAEs was significantly higher in the tramadol ER group. Significantly more nausea, vomiting, and dizziness was reported with tramadol ER (1 RCT, 235 patients;[15] SOE: Low).

Tramadol Versus Placebo (short-term study)

- Safety: Significantly more AEs occurred in the tramadol group than placebo, and the drop-out rate was higher for tramadol. All common AEs (e.g., tiredness, dry mouth, dizziness, sweating, constipation, nausea) occurred more frequently with tramadol (1 RCT, 35 patients;[17] SOE: Very low).

Our searches did not identify any studies that met our inclusion for follow-up (≥3 months) that compared an opioid of interest with other treatment modalities. We are also unable to determine the comparative effectiveness and safety of COT for patients with a history of or current SUD due to the exclusion of these patient populations in studies included in this key question.

Overview of Evidence Base

Of the 18 included studies, 12 studies evaluated opioids versus placebo for at least 3 months. Of these 12 studies, 11 are RCTs and 1 is a systematic review (Santos et al. 2015)[1] that included 3 RCTs. (RCTs).[2-12] 3 studies (1 systematic review[1] and 2 RCTs[2,3]) evaluated tapentadol ER. Two studies each evaluated BTDS,[11,12] hydrocodone ER,[4,5] OROS hydromorphone ER,[8,9] and oxycodone ER.[6,7] Lastly, one study evaluated FBT.[10] Patient populations were mostly opioid-experienced individuals with low back pain (LBP) (4 RCTs[5,7,9,12]), osteoarthritis (OA) (3 RCTs[6,8,11]), diabetic peripheral neuropathy (DPN)(2 RCTs[2,3]),

OA and LBP (1 review[1] and 1 RCT[4]), and non-cancer related pain (1 RCT[10]). Two studies evaluating BTDS versus placebo enrolled only opioid-naïve individuals.[11,12] Five studies were published in 2014 to 2015[1,3-5,7] while seven studies were published in 2010 to 2011[2,6,8-12] Of the 14 primary studies, 12 (86%) studies were conducted over 12 weeks; 1 study included in the Santos review was 15 weeks and 1 study was 6 months.[11]

Due to short term follow-up (less than 3 months), we only include information on the safety of opioids versus placebo from 6 studies. Opioids of interest in these studies include tramadol (4 RCTs),[13-15,17] BTDS (1 RCT),[16] and CR oxycodone/CR naloxone (1 RCT).[18] Patient populations were opioid naïve,[13] mostly opioid naïve[15,17] or mostly opioid-experienced individuals[14-16,18] with LBP (5 studies[13-16,18]) and neuropathic pain after spinal cord injury (SCI)(1 study[17]). Follow-up ranged from 2 weeks to 8 weeks. We excluded 17 studies related to this key question. A list of these studies with exclusionary reasons are presented in Table 4.

Study Quality Rating

We assessed the risk of bias of individual studies using the U.S. Preventive Services Task Force (USPSTF) criteria. Two RCTs addressing long-term use of BTDS versus placebo were rated as Poor.[11,12] Both RCTs had follow-up of fewer than 80% of patients. One RCT also had treatment groups with dissimilar clinical characteristics (i.e., pain scores on the WOMAC OA index) at baseline.[11] The other RCT did not use an intent-to-treat analysis for all outcomes.[12] One study included for short-term safety for BTDS versus placebo[16] was rated as Fair because fewer than 80% of patients were followed up for the duration of the study.

One RCT evaluating FBT versus placebo was rated as Fair mostly due to <80% follow-up of patients.[10] The two RCTs addressing hydrocodone versus placebo were rated as Fair.[4,5] Neither group had follow-up on 80 percent or more of patients. One RCT did not describe randomization or allocation methods.[5] Two RCTS addressing OROS hydromorphone versus placebo were rated as Fair.[8,9] Both studies had less than 80% follow-up of patients.

One RCT addressing short-term safety for CR oxycodone/CR naloxone versus placebo[18] was rated as Good due to performing intent-to-treat (ITT) analysis; adequate blinding, randomization and allocation concealment; and low attrition. Both RCTs addressing oxycodone ER versus placebo were rated as Fair.[6,7] Follow-up for both studies was less than 80%; one study[6] did not describe randomization and allocation methods.

The overall quality of the studies included in the one systematic review[1] on tapentadol ER was rated as Fair. The review authors noted that two studies had a low risk of bias due to incomplete outcome data while one study had a high risk of bias due to concerns regarding the outcomes selected and lack of an allocation concealment description. The 2 RCTs evaluating tapentadol with placebo were rated as Fair[2,3] which was mostly due to lack of follow-up on more than 80 percent of patients.

Three RCTs addressed short-term safety outcomes for tramadol ER versus placebo.[13-15] One of these RCTs also compared tramadol ER to flupirtine, a centrally acting nonopioid analgesic.[15] Two studies were rated as Fair.[3,15] Both studies had less than 80% follow-up for at least one group. One study was rated as Good.[13]

Lastly, one study addressing short-term safety outcomes for tramadol versus placebo[17] was rated Poor because the follow-up rate greatly varied between groups and was less than 80% for the tramadol group. Additionally, patients with paraplegia and tetraplegia were not evenly distributed between treatment groups—more patients with paraplegia than tetraplegia were randomly assigned to the placebo group. Patients were allowed to continue previously stable doses of opioids during the study, which may have confounded outcomes.

Overview of Study, Patient, and Intervention Characteristics

Below we provide a brief description of the study, patient, and intervention characteristics of the studies that make up the evidence base on opioids versus no opioid therapy. We present information on the long-term studies followed by information on the short-term safety studies. Further details are provided in Table 2, Table 3-a, and Table 3-b.

Studies Addressing Long-term Effectiveness and Safety

Buprenorphine Transdermal Delivery System Versus Placebo

Two RCTs addressing this comparison[11,12] enrolled opioid-naïve patients with chronic pain. Patients were initially treated with 5µg/h of BTDS (BuTrans™, Purdue Pharma, Pickering, Canada). Patients were titrated up to 10- or 20 µg/h as needed. Breivik et al. 2010[11] evaluated the efficacy and tolerability of BTDS, added to a nonsteroidal anti-inflammatory drug (NSAID) or COX-2-selective inhibitor regimen, in 199 patients (100 BTDS, 99 placebo) with osteoarthritis (OA) pain of the hip or knee for at least 1 year. The majority of patients had OA in the knee (63.3%). Eight patients in each group had very severe radiographic OA, and the rest had moderate or severe OA. Mean age was approximately 63 years for both groups. More female patients were included in both groups (72.00% BTDS, 64.65% placebo). Patients were taking NSAIDs or COX-2-selective inhibitors for their OA pain for at least 1 month before enrolling in the study and continued on stable doses throughout the study. Patients had not been previously treated with strong opioids; weak opioid use (e.g., tramadol, codeine) was acceptable if it was intermittent, continued for less than 3 weeks prior to the study, and was discontinued for the duration of the study. Patients with a history of alcohol or substance abuse, as determined by the investigator, were excluded. Patients were evaluated for 6 months. The primary efficacy outcome was change in the WOMAC OA index pain subscale score from baseline to 6 months or withdrawal from study.

Steiner et al. 2011[12] evaluated the efficacy, tolerability, and safety of BTDS in 541 patients (257 BTDS, 284 placebo) with moderate-to-severe LBP for more than 3 months. Mean age was about 50 years. Both groups had more female patients (52% BTDS, 58% placebo). Patients with nonmalignant causes (e.g., intervertebral disc disease, spinal stenosis, spondylolysis, spondylolisthesis, OA) of LBP were included. Patients were excluded if they received more than 5 mg of oxycodone (or equivalent) in the 14 days before enrolling, had a history of daily use of 5 mg or more of oxycodone (or equivalent) for 3 months before screening, or were considered by the investigator to be opioid-dependent. The investigators gave patients acetaminophen (APAP) and ibuprofen for supplemental analgesia as needed. Patients were followed for 12 weeks. The primary efficacy outcome was average pain over the last 24 hours at week 12 using an 11-point numerical rating scale (NRS).

Fentanyl Buccal Tablets Versus Placebo

One RCT (Farrar et al. 2010[10]) addressing this topic evaluated 79 opioid-tolerant adults (used as their own controls) with non-cancer-related breakthrough pain (BTP). The most commonly reported source of chronic pain was back pain (47%), neck pain (11%), and complex regional pain syndrome (9%). Mean age was 51 years with fewer males (37%) than females (63%). Patients experiencing 1 to 4 episodes of BTP per day were enrolled. BTP was defined as temporary flares of severe or excruciating pain, each lasting <4 hours, and that were at least partially relieved by their current supplemental opioid. Eligible patients had to be opioid tolerant, defined as receiving ≥60 mg/day of oral morphine, ≥25 µg/hour of transdermal fentanyl, ≥30 mg/day of oxycodone, ≥8 mg/day of hydromorphone, or an equivalent, stable daily dose of another opioid for ≥30 days before enrolling in the study. Individuals with a history of alcohol or other substance abuse during the past 5 years were excluded. Adequate pain relief was attained in most patients during the titration phase with the 2 highest doses of FTB (800 µg [49%] and 600 µg [23%]).

Hydrocodone Extended Release versus Placebo

Two RCTs addressing this comparison[4,5] allocated patients with chronic pain ≥3 months to hydrocodone ER tablets (doses ranging from 15–100 mg) or matching placebo every 12 hours. Hale et al. 2015[4] evaluated the efficacy of hydrocodone bitartrate (Teva Pharmaceuticals, Frazer, PA) with CIMA® Abuse-Deterrence Technology in 293 patients (146 hydrocodone ER, 147 placebo) with moderate-to-severe chronic pain due to OA or LBP. Over 70% of each group suffered from LBP. Mean duration since diagnosis was over 12 years in each group (12.1±10.0 hydrocodone, 12.5±9.1 placebo). Mean age was approximately 53 years in each group; more patients were female (60% hydrocodone, 59% placebo). The study population was made up of both opioid-naïve and opioid-experienced individuals. Average pain intensity score ≥5 on an 11-point NRS during the previous 24 hours was required. Individuals with a recent history (≤5 years) or current evidence of alcohol or other substance abuse (except nicotine or caffeine), or were taking >135 mg/day of oxycodone, or equivalent, during the 14 days before screening were excluded. Doses of hydrocodone ER were as follows: 27% 30 mg/day, 26% 60 mg/day, 22% 90 mg/day, and 11% 180 mg/day. During the first 2 weeks of the double-blind period, supplemental analgesia (hydrocodone/acetaminophen [HC/APAP] 5 mg/325 g every 4 to 6 hours [total daily hydrocodone dose of 30 mg]) was permitted. During week 3 to study end, patients were permitted HC/APAP tablets 5 mg/325 mg as needed [total daily hydrocodone dose of 10 mg]). NSAIDs were also permitted on an as-needed basis (e.g., ibuprofen at a maximum dosage of 2,400 mg/day). The primary efficacy outcome was change from baseline (final visit of the open-label titration period) to week 12 in the mean weekly average pain intensity (API: 0=no pain, 10=worst pain imaginable).

The other RCT (Rauck et al. 2014[5]) enrolled 302 opioid experienced individuals (151 hydrocodone ER [HC-ER], 151 placebo) with chronic LBP (CLBP). Mean age of patients was 50 years; percent males was higher in the placebo arm (38.4% HC-ER, 51% placebo). Individuals were mostly white (81.5% HC-ER, 79.5% placebo) with an average PI score of 3.1 points after titration (3.1±0.9 HC-ER, 3.1±1.0 placebo). Individuals were required to have an average pain score of ≥4 on the NRS for the past 24 hours of screening (prior to baseline). History of opioid abuse or illicit drug or alcohol abuse in the past 5 years was an exclusionary criterion. Patients received Zohydro® ER (Zogenix, Inc., San Diego, CA) as 10-, 20-, 30-, 40- and 50-mg capsules or matching placebo. Mean total daily dose (TDD) was 119 mg with doses ranging from 40 to 200 mg/day. Rescue medicine (a maximum of 2 tablets of HC 5 mg/APAP 500 mg per day) was allowed for both treatment groups throughout the treatment period. During days 15 to 85 (drug tapering

completed), use of rescue medicine was slightly higher in the placebo group (0.9±0.6 HC-ER, 1.1±0.6 placebo). The primary efficacy outcome was mean change in API from baseline to day 85 on the 11-point NRS.

OROS Hydromorphone Hydrochloride Versus Placebo

Two RCTs addressed this comparison.[8,9] Vojtassak et al. 2011[8] enrolled 288 patients (139 OROS hydromorphone, 149 placebo) to evaluate the efficacy of OROS hydromorphone (Exalgo, Mallinckrodt Inc., a Covidien company, Hazelwood, MO) for treating moderate-to-severe OA pain in the hip or knee. Most patients had knee pain (74%). The mean NRS pain score at baseline was 3.2±1.0. Mean age was about 65 years. Both groups had more female patients (77% OROS hydromorphone, 68% placebo). Patients who were taking an opioid in the 4 weeks before screening, except for infrequent use of tramadol, codeine, tilidine, or dihydrocodeine for no more than 10 days, were excluded. OROS hydromorphone dosages were titrated until satisfactory pain control was reached; doses ranged from 4 mg to 32 mg per day. Patients on weak opioids discontinued their use before the study. Patients continued to take NSAIDs or paracetamol at stable doses. Paracetamol (up to 4 g until day 8; up to 2 g for the rest of the study) was given as rescue medication. Patient follow up was 16 weeks. The primary efficacy outcome was mean change from baseline to week 16 in "pain on average" on the Brief Pain Inventory (BPI) scale.

Hale et al. 2010[9] enrolled 266 patients (133 OROS hydromorphone, 133 placebo) to evaluate the efficacy and safety of OROS hydromorphone in treating chronic moderate-to-severe LBP. Patients had LBP for at least 3 hours per day, 20 days per month, for 6 months. The mean baseline "pain on average" scores were 6.6±1.04 for OROS hydromorphone and 6.5±0.94 for placebo. Patients must have been on daily opioid treatments of 60 mg or more oral morphine equivalent (≥12 mg hydromorphone) but 320 mg or less oral morphine equivalent (≤64 mg hydromorphone) within 2 months before the initial screening visit to be included. Analgesic doses were titrated or converted to a daily OROS hydromorphone dose (≥12 mg and ≤64 mg) that was about 75% of the equianalgesic dose of their previous total daily opioid dose. The median (range) daily dose of medication was 12.2 (3–28) mg for OROS hydromorphone and 20.1 (4–29) mg for placebo. Hydromorphone immediate release (2-, 4-, or 8 µg) was given as rescue medication. Patient follow up was 12 weeks. The primary efficacy outcome was mean change from baseline to week 12 or final visit in weekly pain intensity NRS scores recorded by patients daily in a paper diary.

Oxycodone Extended Release Versus Placebo

2 RCTs addressed this comparison.[6,7] The first RCT (Katz et al. 2015[7]) allocated 389 opioid-naïve and opioid-experienced patients with moderate-to-severe CLBP to an abuse-deterrent formulation of extended-release oxycodone (Xtampza ER – oxycodone using the DETERx drug delivery platform) or placebo. Mean age was 49 years; 50% of the population was male. Baseline scores for physical and mental component subscales for Short-form 12, version 2 (SF-12v2) and Roland-Morris Disability Questionnaire (RMDQ) were comparable. Opioid-experienced patients were defined as patients on a daily dose of opioid medication ≥30 and ≤240 mg/day of morphine sulfate equivalents for a minimum of 14 days before the screening visit. Opioid-naïve patients were on 0 to 10 mg/day morphine sulfate equivalent for 14 days or more before the screening visit. Patients who were on an opioid regimen for <14 days as well as patients with a known history of alcohol or drug abuse, major depressive disorder that was not controlled with medication, or other conditions that produced significant cognitive or emotional disability were excluded. Patients in the Xtampza ER group were taking 20-, 30-, 40-, 60-, or 80 mg every 12 hours. The placebo group were taking matching active drug containing identical microspheres with the exception of oxycodone

every 12 hours. APAP was available as rescue medication. Primary efficacy outcome (change in API) was evaluated at 12 weeks. A follow-up phone call was made at 14 weeks.

The second RCT (Friedmann et al. 2011[6]) assessed the safety and efficacy of Remoxy versus placebo in 412 patients (205 Remoxy, 207 placebo) with a diagnosis of moderate-to-severe chronic pain due to osteoarthritis (OA) of the hip (22% Remoxy, 21% placebo) and OA of the knee (78% Remoxy, 79% placebo). The patient population was mostly females (72% Remoxy, 68% placebo) aged 50 years to 60 years (58±7.86 Remoxy, 58.5±8.44 placebo). Pre-randomization pain intensity scores were similar at baseline (5.2±2.19 Remoxy, 5.4±2.11 placebo). The pre-randomization WOMAC Osteoarthritis Index total score was higher in the placebo group (1,170.2±566.69 Remoxy, 1,194.8±553.78 placebo). Included patients were regularly (≥4 days/week every week for 4 weeks prior to the screening visit) taking one or more of the following oral medications: nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, tramadol, and opioids. Individuals with a positive urine drug screen for opiates, amphetamines, methamphetamines, cocaine, cannabinoids, phenylcyclohexylpiperidine, or methadone at the baseline visit were excluded. Maximum Remoxy allowed was 40 mg twice daily (bid), minimum allowed 5 mg bid. Supplemental analgesia (aspirin for cardiovascular events) was allowed. The primary efficacy outcome was area under the curve for the change in PI score from pre-randomization to double-blind week 12.

Tapentadol Extended Release Versus Placebo

One systematic review (Santos et al. 2015[1]) and two RCTs (Vinik et al. 2014,[3] Schwartz et al. 2011[2]) compared the effectiveness of tapentadol ER with placebo. The evidence base for the 2015 review[1] was 3 RCTs that enrolled 1,989 patients (987 tapentadol ER, 1,002 placebo) with knee osteoarthritis (2 studies enrolling 1,342 patients) or low back pain (1 study enrolling 647 patients). All studies enrolled adults aged 18 years or older with moderate-to-severe chronic pain (at least 3 months) of any cause. One study enrolled patients aged ≥40 years; 2 studies did not report age. Tapentadol ER was administered in 200 to 500 mg/day. Follow-up was 12 weeks in two studies and 15 weeks in one study.

Both RCTs (Vinik et al. 2014[3] and Schwartz et al. 2011[2]) were 12 week studies that evaluated tapentadol ER for managing chronic pain associated with diabetic peripheral neuropathy (DPN). Both studies enrolled patients with type 1 or 2 diabetes and chronic painful DPN for ≥6 months. The first study (Vinik et al. 2014[3]) enrolled 318 patients; randomly allocating 166 individuals to tapentadol ER and 152 patients to placebo. Overall mean age of patients was approximately 59 years. Male gender was 59.6% in the tapentadol ER group and 57.9% in the placebo group. Dose categories for tapentadol group were 100–150 mg bid or 200–250 mg bid. Placebo was identical in appearance and packaging to tapentadol. All participants were permitted tapentadol ER 25 mg bid for additional analgesia during the first 4 days of the double-blind phase of the study; and once per day from day 5 to study end (12 weeks). Patients with conditions that could confound the assessment of pain (e.g., fibromyalgia, rheumatoid arthritis) were excluded.

The second RCT (Schwartz et al. 2011[2]) enrolled 389 patients (196 tapentadol ER, 193 placebo). Overall mean age was approximately 60 years. Male gender was 60% in both arms. The mean duration of DPN (in weeks) was higher in the placebo arm (284.90±258.85 tapentadol, 317.96±261.61 placebo). Tapentadol ER was administered in a fixed optimal dose of 100–250 mg bid. The placebo group received blinded tapentadol ER 100 mg bid for 3 days before switching to placebo to minimize possible withdrawal related to discontinuation. Supplemental analgesia was permitted in a similar fashion as the Vinik study.

Primary efficacy outcome for both studies was mean change in average pain intensity (API) from baseline (start of double-blind phase) to week 12 based on an 11-point numeral rating scale.

Studies Addressing Short-term Safety

Below we provide a brief description of the study, patient, and intervention characteristics of the short-term studies that provide additional evidence for the safety of opioids. Additional information is provided in Table 3-b.

Buprenorphine Transdermal Delivery System Versus Placebo

One short-term RCT addressed this comparison. Gordon et al. 2010[16] enrolled 78 patients (39 BTDS, 39 placebo) in a crossover trial. Mean age was about 50 years. More female patients were included (60.3%). Patients were included who had chronic LBP of at least moderate intensity for 3 months or more and required 1 or more daily tablets of an opioid analgesic. At baseline, mean daily pain intensity was 60.9±15.4 mm on a 100-mm visual analog scale (VAS). Patients with pain refractory to opioids were excluded. The BTDS dosage was 10 µg/h for 6-8 days, titrated weekly to a maximum of 40 µg/h. Investigators provided 325-750 mg acetaminophen to be taken every 4-6 hours as needed. Patients were also permitted to continue using nonopioid analgesics at stable doses. Follow-up was 8 weeks.

Controlled Release Oxycodone/Controlled Release Naloxone Versus Placebo

One RCT (Cloutier et al. 2013[18]) reported on this comparison in 83 patients (39 CR oxycodone/CR naloxone, 44 placebo). Patients had at least moderate chronic LBP for 3 months or longer, and a mean age of about 51 years. Females represented 53% of the patients. Patients who were taking opioids prior to the study or who were not but required opioids for pain control were included. Before the study, 90.4% of patients were taking opioids for chronic LBP. Patients who required more than 360 mg of codeine daily, had pain expected to be refractory to opioids, or had a known or suspected psychological dependence on narcotic analgesics, other psychoactive drugs, or excessive consumption of alcohol were excluded. Patients were administered 10 mg/5 mg CR oxycodone/CR naloxone (Targin, Purdue Pharma, Pickering, Canada) every 12 hours initially. They were titrated weekly according to pain control and side effects to 20/10-, 30/15-, or 40 mg/20 mg CR oxycodone/CR naloxone every 12 hours. Investigators provided 300 mg/30 mg APAP/codeine tablets for unrelieved pain (patients were permitted to take 1-2 tablets every 4 hours as needed) and 8.6 mg senna/docusate sodium tablets for constipation as needed. Patients were permitted to continue stable doses of nonopioid analgesics during the study. The crossover study had a treatment period of 8 weeks and an open-label extension phase of 6 months.

Tramadol Extended Release Versus Placebo

Three RCTs addressed tramadol ER versus placebo in patients with chronic LBP.[13-15] Hyup Lee et al. 2013[14] enrolled 245 patients (125 tramadol ER, 120 placebo). Patients received 75 mg of tramadol ER (Ultracet®, Janssen-Ortho, LLC, Gurabo, Puerto Rico) daily for 3 days, then 75 mg twice daily for 4 days, and then 75-150 mg twice daily depending on their levels of pain control for 22 days. Total follow-up time was 29 days. Mean age was about 60 years. Both groups had more females (75.2% tramadol ER, 74.2% placebo). Investigators enrolled patients with an average pain intensity of 4 or greater on a 10-cm VAS and on stable, but inadequate, doses of NSAIDs or COX-2-selective inhibitors for at least 7 days before the study. Patients continued on their stable doses of NSAIDs or COX-2-selective inhibitors for the duration of

the study. Patients who previously used tramadol or opioid analgesics within 30 days of the study were excluded.

Schiphorst Preuper et al. 2014[13] studied this comparison in 50 patients (25 tramadol ER, 25 placebo) with chronic LBP for more than 3 months. Investigators enrolled patients who had pain of 4 or more on the VAS. Patients who were using opioids were excluded. Tramadol ER (ACE Pharmaceuticals, Zeewolde, the Netherlands) was administered at 37.5 mg twice daily or 75 mg thrice daily. Supplemental analgesia was not allowed. Total follow-up time was 2 weeks.

Uberall et al. 2012[15] allocated 355 patients to three groups. In this comparison, 116 patients received 200 mg tramadol ER (not specified) daily, and 120 patients received matching placebo (see tramadol ER versus flupirtine below). Mean age was about 58 years. Both groups had more female patients (61.2% tramadol ER, 55.8% placebo). Patients enrolled had average baseline pain intensity (11-point NRS) of 5.85±1.21 in the tramadol ER group and 5.94±1.44 in the placebo group. Patients with alcohol, analgesic, narcotic, or other substance abuse within the past 2 years were excluded. Diclofenac natrium tablets were provided as supplemental analgesia to be taken as needed up to 150 mg per day. The follow-up period was 5 weeks.

Tramadol Extended Release Versus Flupirtine

Uberall et al. 2012[15] also compared tramadol ER versus flupirtine (not specified), a nonopioid analgesic. Patients in the tramadol ER group were described previously. Patients in the flupirtine group (119) had a mean age of about 58 years, and 68.9% were female. They had an average baseline pain intensity (11-point NRS) of 5.72±1.25. Inclusion and exclusion criteria were previously described. Follow-up was 5 weeks.

Tramadol Versus Placebo

One RCT (Norrbrink and Lundeberg 2009[17]) compared an unspecified formulation of tramadol (Lannacher Heilmittel GesmbH, Lannach, Austria) with placebo in patients with traumatic and non-traumatic SCI and neuropathic pain at or below the level of injury. Investigators enrolled 35 patients (23 tramadol, 12 placebo) with a mean age of about 51 years. Patients were mostly male in both groups (82.6% tramadol, 75% placebo). Patients who had previously taken tramadol were excluded. Median general pain intensity on Borg's Category Ratio 10-point scale at baseline was 4 for the tramadol group and 7 for the placebo group. Patients were administered 50 mg tramadol thrice daily, which was increased by 50 mg every 5 days until 400 mg daily or optimal pain relief was obtained. Patients continued stable doses of medication that they were taking prior to the study. Medications included opioids (22% tramadol, 17% placebo) and NSAIDs/COX-2-selective inhibitors (9% tramadol, 17% placebo). Additional supplemental analgesia was not given. Follow-up time was 4 weeks.

Outcomes and Synthesis of Results

Below we provide an overview of the main findings of the studies. Additional information and results are provided in Table 1-a and Table 1-b.

Studies Addressing Long-term Effectiveness and Safety

Buprenorphine Transdermal Delivery System Versus Placebo

Two RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12]) addressed this comparison. Both RCTs reported pain on an 11-point NRS, daily rescue medication use, and several adverse events. Other outcomes were reported by only one study.

Pain (NRS-11): Both RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12]) reported significantly greater reductions in pain intensity with BTDS (Breivik: Difference between means -0.5 [95% CI: -0.95 to -0.05; p=0.0292]; Steiner: Difference between means -0.58 [95% CI: -1.02 to -0.14; p=0.0104]).

WOMAC OA pain subscale: One RCT (Breivik et al. 2010[11]) reported no significant between-group difference (Difference -0.86 [95% CI: -1.76 to 0.04; p=0.061]).

WOMAC OA stiffness subscale: One RCT (Breivik et al. 2010[11]) reported no significant between-group difference (Difference -0.18 [95% CI: -0.56 to 0.19; p=0.331]).

WOMAC OA functional ability subscale: One RCT (Breivik et al. 2010[11]) reported no significant between-group difference (Difference -2.90 [95% CI: -5.86 to 0.06; p=0.055]).

WOMAC OA overall score: One RCT (Breivik et al. 2010[11]) reported no significant between-group difference (Difference -3.95 [95% CI: -8.06 to 0.16; p=0.0592]).

Daily rescue medication use: Both RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12]) reported no significant between-group differences (Breivik: Mean of 2 tablets of 0.5 g paracetamol per day for all patients; Steiner: Difference -0.124 (95% CI: -0.296 to 0.048; p=0.1586)).

Number of nights woken because of pain: One RCT (Breivik et al. 2010[11]) reported no significant between-group difference (p=0.8542).

Quality of sleep (5-point scale): One RCT (Breivik et al. 2010[11]) reported no significant between-group difference.

Sleep disturbance (subscale MOS Sleep Scale): One RCT (Steiner et al. 2011[12]) reported significantly less sleep disturbance with BTDS (Difference -4.4 [95% CI: -7.5 to -1.3; p=0.0062]).

Patient Global Impression of Change (PGIC): One RCT (Breivik et al. 2010[11]) reported a significantly greater improvement in PGIC with BTDS (p=0.0171).

Time until completion of study or withdrawal: One RCT (Breivik et al. 2010[11]) reported patients withdrew from treatment earlier with BTDS (157 days BTDS [164 for hip, 143 for knee]; 167 days placebo [almost identical for hip and knee]). Additionally, "None of the following variables analysed had a significant effect on the treatment duration: primary site of pain, i.e. knee or hip (p=0.3617); adverse events (p=0.2618); seasons (p=0.9872); patient gender (p=0.1207), or the WOMAC score for pain at baseline (p=0.3928)."[11]

Incidence of AEs: One RCT (Breivik et al. 2010[11]) reported more AEs with BTDS (92.0% BTDS, 73.7% placebo).

Constipation: Both RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12]) reported more constipation with BTDS (Breivik: 24.0% BTDS, 5.1% placebo; Steiner: 4% BTDS, 1% placebo).

Nausea: Both RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12]) reported more nausea with BTDS (Breivik: 37.0% BTDS, 10.0% placebo; Steiner: 13% BTDS, 11% placebo).

Vomiting: Both RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12]) reported more vomiting with BTDS (Breivik: 16.0% BTDS, 2.0% placebo; Steiner: 4% BTDS, 2% placebo).

Dizziness: Both RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12]) reported more dizziness with BTDS (Breivik: 25.0% BTDS, 9.1% placebo; Steiner: 4% BTDS, 1% placebo).

Headache: Mixed results for this outcome. Breivik et al. 2010[11] reported more headache with BTDS (7.0% BTDS, 6.1% placebo) while Steiner et al. 2011[12] reported no difference (5% BTDS, 5% placebo).

Drop-out rate due to AEs: Both RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12]) reported more patients dropped out due to AEs in the BTDS group (Breivik: 31% BTDS, 2% placebo; Steiner: 16% BTDS, 7% placebo).

Incidence of serious AEs: Both RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12]) reported similar incidences of serious AEs (Breivik: 5% BTDS, 4% placebo; Steiner: 1.1% BTDS, 0.7% placebo).

Incidence of TEAEs: One RCT (Steiner et al. 2011[12]) reported a similar incidence of TEAEs in both groups (55% BTDS, 52% placebo).

Loss to follow-up: One RCT (Steiner et al. 2011[12]) reported 1 patient in the BTDS group was lost to follow-up during the double-blind phase (out of 541 total).

Fentanyl Buccal Tablets Versus Placebo

Farrar et al. 2010[10] reported significant findings in favor of FBT for all primary and secondary outcomes.

Pain ($SPID_{60}$): Sum of the pain intensity difference 60 minutes post-dose was significantly greater for BTP episodes treated with FBT compared with placebo after week 12 (mean±SD 7.7±6.2 FBT, 4.6±4.7 placebo; $p<0.001$). Similar findings were demonstrated (after week 12) 30 minutes after drug administration (2.8±2.8 FBT, 1.6±2.0; $p<0.01$), 90 minutes after drug administration (12.9±9.6 FBT, 7.5±7.5 placebo; $p\leq0.001$), and 120 minutes after drug administration (18.2±13.1 FBT, 10.4±10.3 placebo; $p\leq0.001$).[10]

Pain (>33% improvement): The proportion of BTP episodes with ≥33% improvement in PI was greater after FBT compared with placebo, beginning at 5 minutes post-dose (7% FBT, 3% placebo; $p=0.0150$) and increasing to a maximum of 90 minutes (54% FBT, 31% placebo; $p<0.0001$).[10]

Pain (>50% improvement): The proportion of BTP episodes with ≥50% improvement in PI reached statistical significance 15 minutes post-dose with FBT compared with placebo (17% versus 10%; $p=0.0216$) and was maintained at all subsequent time points.[10]

Pain relief (PR): The average onset of PR began at 5 minutes (12% FBT, 7% placebo; $p=0.0175$), with meaningful PR by ≤10 minutes (14% FBT, 7% placebo; $p=0.0006$).[10]

Supplemental medication: Supplemental medication was used in fewer BTP episodes treated with FBT compared with episodes treated with placebo (26% FBT treated, 40% placebo treated; Odds ratio (OR) 1.8640 (95% CI: 1.3 to 2.7; p=0.0007).[10]

Discontinued due to AEs (overall): 10% (6% dose titration phase, 4% 12-week treatment phase)

AEs: Nausea (15%), dizziness (11%), somnolence (8%), vomiting (5%), arthralgia (5%), back pain (4%), gastroenteritis viral (4%), influenza (4%), and constipation (3%).

Application-site AEs (overall): 7%; erythema (4 patients), swelling (2 patients), erythema and discoloration (1 patient), erythema and vesicles (1 patient), and irritation, reaction, and ulcer (1 patient each).

TEAEs (overall): 45%

Serious AEs: 7%; pneumonia (2 patients), obliterative bronchiolitis, pyelonephritis, abuse of study medication, panic attack, biliary dilatation, neuropathic pain, device-related infection, osteomyelitis, and multiple drug overdoses occurred in 1 patient each. Accidental overdose occurred in 1 patient who developed pneumonia. The authors noted that "it is not known what the relative contributions of study medication or other opioids were to these events."

Drug abuse: 1 patient consumed all their opioid medication (FBT, oxycodone, and Oxycocet) over a short period of time and suffered withdrawal symptoms after finishing her medications.

Hydrocodone Extended Release Versus Placebo

Both RCTs addressing this comparison reported on pain intensity, however, the majority of remaining outcomes (e.g., function, quality of life) were reported on by only one study.

Pain intensity (11-point NRS): Results were mixed for this outcome. While one RCT reported significant between group differences favoring hydrocodone for higher reduction in pain intensity compared with placebo at day 85,[5] the other study reported no significant difference (p=0.134) for mean change in API at week 12.[4] Post hoc analysis in this study[4] did indicate that the change in weekly API was significantly lower with hydrocodone ER when excluding the lowest dose (15 mg); least squares mean (LSM) -0.20 HC-ER versus 0.40 placebo; p=0.032).

Response (≥50% average PI score improvement): Significantly more responders were demonstrated in the HC-ER group at day 85 (48% HC-ER, 23% placebo; p<0.001) in Rauck et al. 2014.[5]

Response (≥30% average PI score improvement): Significantly more responders were demonstrated in the HC-ER group at day 85 (68% HC-ER, 31% placebo; p<0.001) in Rauck et al. 2014.[5]

Response (50% increase from baseline in weekly API): Significantly more patients receiving placebo had >50% increase in weekly API at week 8 (18% versus 6%; p=0.005) and week 12 (15% versus 6%; p=0.041) in Hale et al. 2015.[4]

Response (33% increase from baseline in weekly API): Significantly more patients receiving placebo had >33% increase in weekly API at week 2 (22% versus 11%; p=0.016) and week 12 (24% versus 11%; p=0.017) in Hale et al. 2015.[4]

Worst pain intensity (WPI): Mean weekly WPI was significantly lower with hydrocodone ER at week 2 (0.27 versus -0.15; p=0.025), week 8 (0.00 versus -0.68; p=0.004) and week 12 (-0.03 versus -0.60; p=0.025) in 1 study.[4]

Function (PAF and CAPF): No significant differences were reported between hydrocodone ER and placebo in a 12-week study (Hale et al. 2015) measuring function with Patient Assessment of Function and Clinical Assessment of Function scales.[4]

Symptom severity: No significant differences were reported between hydrocodone ER and placebo in a 12-week study (Hale et al. 2015).[4]

Pain (BPI-SF [Brief Pain Inventory-Short Form]): No significant differences were reported between hydrocodone ER and placebo in a 12-week study (Hale et al. 2015).[4]

Quality of life (SF-36 [Short-form 36]): No significant differences were reported between hydrocodone ER and placebo in a 12-week study (Hale et al. 2015).[4]

Satisfaction (SGAM [Subject Global Assessment of Medication (SGAM]): Significantly more HC-ER patients were satisfied with pain medication at day 85 compared with placebo patients (0.8±1.3 HC-ER, 0.0±1.4 placebo; p<0.001) in a 85 day study (Rauck et al. 2014).[5]

Supplemental analgesia: Hale et al. 2015[4] reported that use of supplemental analgesia was higher with placebo (86% versus 79%). From weeks 1 to week 12, mean daily dose of opioid rescue medicine (hydrocodone equivalent dose) ranged from 2.2 mg to 5.4 mg and 2.0 mg to 3.5 mg for the placebo and hydrocodone groups, respectively.

Withdrawal: Results were mixed for this outcome. While one study[5] reported significantly more placebo patients experienced withdrawal syndrome (0.7% HC-ER, 6% placebo; p<0.019), the other study reported similar withdrawal between groups at each visit.[4]

Aberrant drug-related behaviors: Hale et al. 2015[4] reported results at three time points. At start of open label, positive results for aberrant drug-use behaviors were reported in 22 patients (15 hydrocodone ER, 7 placebo). At week 2, a low risk of aberrant drug-related behavior was reported for 71% hydrocodone ER and 78% placebo patients. At study endpoint, there was no indication of aberrant drug-use behavior in 210 patients (100 hydrocodone ER, 110 placebo patients).

Inappropriate opioid use behaviors: Hale et al. 2015[4] reported results at two time points. At start of open label, positive results for inappropriate opioid use behavior were reported in 3 patients (2 hydrocodone ER, 1 placebo). At study endpoint, there was no indication of inappropriate opioid use in 212 patients (101 hydrocodone, 111 placebo).

Diversion: 4 patients; 3 reported theft of rescue medication, 1 returned unknown medication instead of hydrocodone ER[4]

Incidence of TEAEs (treatment phase): Rauck et al. 2014[5] reported significantly more HC-ER patients experienced at least 1 TEAE (60% HC-ER, 44% placebo; p=0.006).

Serious TEAE: Hale et al. 2015[4] reported that 2 episodes of acute pancreatitis occurred in 1 hydrocodone patient. The patient eventually developed chronic pancreatitis.

TEAEs (conversion/titration phase): Constipation (11%) and nausea (9.8%) were the most commonly reported TEAEs reported by Rauck et al. 2014.[5] Other TEAEs occurring in this population of 510 randomized and nonrandomized patients included somnolence (4.7%), fatigue (4.1%), headache (3.7%), dizziness (3.3%), dry mouth (3.1%), vomiting (2.7%), pruritus (2.5%), insomnia (2.4%), diarrhea (2.2%), back pain (0.8%), urinary tract infection (0.8%), withdrawal syndrome (0.6%), hypoacusis (0.6%), and sinusitis (0.4%).

TEAEs (treatment phase): During the treatment phase, Rauck et al. 2014[5] reported that significantly more HC-ER patients experienced at least 1 TEAE (60% HC-ER, 44% placebo; p=0.006). Significant between group differences were also reported for incidence of constipation (7.9% HC-ER, 0% placebo; p<0.001) and withdrawal symptom (0.7% HC-ER, 6.0% placebo; p=0.019). Other TEAEs reported included nausea (7.3% HC-ER, 3.3% placebo), somnolence (0.7% HC-ER, 0% placebo), fatigue (0.7% HC-ER, 1.3% placebo), headache (0% HC-ER, 1.3% placebo), dizziness (2.0% HC-ER, 0.7% placebo), vomiting (4.6% HC-ER, 0.7% placebo), insomnia (2.0% HC-ER, 4.6% placebo), diarrhea (2.6% HC-ER, 5.3% placebo), back pain (4.0% HC-ER, 3.3% placebo), UTI (5.3% HC-ER, 2.0% placebo), hypoacusis (3.3% HC-ER, 2.6% placebo) and sinusitis (2.0% HC-ER, 2.6% placebo).

Discontinuation due to TEAEs: Rauck et al. 2014[5] reported more patients receiving placebo discontinued due to TEAEs than receiving HC-ER (9 placebo [4 from withdrawal], 2 HC-ER).

TEAEs leading to discontinuation: During the conversion/titration phase of 1 study, nausea, constipation, and vomiting caused in 1% to 3% of patients to discontinue the study.[5] During the treatment phase in this same study, back pain and diarrhea caused 1 HC-ER patient each to discontinue. Nine placebo patients also discontinued during this phase; 4 due to withdrawal syndrome, 5 not specified.

Serious AEs (double-blind): During the double-blind phase of Hale et al. 2015,[4] serious adverse events occurred in 6 patients (3 [2%] each group).

AEs (double-blind): During the double-blind phase of Hale et al. 2015,[4] AEs occurred in 64% of hydrocodone and 62% of placebo patients. The following AEs were reported: nausea (6% placebo, 13% hydrocodone), headache (5% placebo, 7% hydrocodone), back pain (5% placebo, <1% hydrocodone), constipation (5% placebo, 13% hydrocodone), upper respiratory tract infection (5% placebo, 5% hydrocodone), vomiting (3% placebo, 6% hydrocodone), dry mouth (1% placebo, 1% hydrocodone), fatigue (1% placebo, <1% hydrocodone), dizziness (<1% placebo, 2% hydrocodone), pruritus (<1% placebo, 2% hydrocodone), somnolence (<1% placebo, 2% hydrocodone).

Discontinuation due to AEs: Results were mixed for this outcome. Rates were higher with hydrocodone ER in one study and lower in another study. (9 hydrocodone ER, 3 placebo [Hale]; 1.3% HC-ER, 3.3% placebo [Rauck]). Rauck et al. reported that one HC-ER patient discontinued participating due to a serious AE (anxiety possibly related to HC-ER) during the conversion/titration phase.

Discontinuation due to efficacy: Rauck et al. 2014[5] reported that 9.3% HC-ER and 42.4% placebo patients discontinued the study due to efficacy.

Discontinuation due to opioid withdrawal: Rauck et al. 2014[19] reported that 4.6% of placebo patients discontinued for this reason.

Discontinuation due to depression: Rauck et al. 2014[19] reported that 0.7% of placebo patients discontinued for this reason.

Loss to follow-up: Rauck et al. 2014[5] reported more HC-ER patients were loss to follow-up than placebo patients (0.7% HC-ER, 0% placebo).

OROS Hydromorphone Hydrochloride Versus Placebo

Mixed results were reported for primary efficacy outcomes for two RCTs (Vojtassak et al. 2011,[8] Hale et al. 2010[9]) addressing this comparison. Only 1 study addressed each outcome except for drop-out rate due to AEs which was reported by both RCTs.

Pain (10-point Brief Pain Inventory [BPI]): One RCT (Vojtassak et al. 2011[8]) reported no significant between-group difference for pain (difference –0.2365 (95% CI: –0.5357 to 0.0627; p=0.1212).

Pain (BPI subscales): One RCT (Vojtassak et al. 2011[8]) reported no significant between-group differences for the BPI subscales "pain at its worst in the last 24 hours," "pain at its least worst in the last 24 hours," and "pain right now."

Pain (11-point NRS diary scores): One RCT (Hale et al. 2010[9]) reported a significantly larger increase in pain intensity in the placebo group (0.2 units OROS hydromorphone, 1.6 units placebo, p<0.001), "indicating that [OROS hydromorphone] provided significantly better pain control"[9] but no reduction in pain.

Pain intensity (weighted mean NRS): One RCT (Hale et al. 2010[9]) reported a significantly larger increase in pain intensity in the placebo group (0.4 units OROS hydromorphone, 1.2 units placebo, p<0.001).

Pain (11-point NRS office scores): One RCT (Hale et al. 2010[9]) reported significantly greater improvements in weekly pain scores recorded in office for the OROS hydromorphone group for every week (p<0.05) except week 3.

Time to treatment failure: One RCT (Hale et al. 2010[9]) reported failure occurred significantly sooner in the placebo group (p<0.001).

WOMAC OA total score: One RCT (Vojtassak et al. 2011[8]) reported no significant between-group difference.

WOMAC OA pain subscale: One RCT (Vojtassak et al. 2011[8]) reported no significant between-group difference.

SF-36 pain subscale: One RCT (Vojtassak et al. 2011[8]) reported no significant between-group difference.

HRQoL: One RCT (Vojtassak et al. 2011[8]) reported no significant between-group difference.

Patient Global Assessment (PGA; 5-point scale): One RCT (Hale et al. 2010[9]) reported significantly improved PGA in the OROS hydromorphone group over placebo (p<0.001).

Functional ability (RMDQ): One RCT (Hale et al. 2010[9]) reported significant between-group differences favoring OROS hydromorphone (p<0.05) for mean weekly changes from baseline in RMDQ scores for weeks 1, 2, 3, 8, and 12 (or final visit) but no significant between-group differences for weeks 4, 6, or 10. A

significant between-group difference was reported favoring OROS hydromorphone (p<0.005) for median change of RMDQ scores from baseline to week 12 (or final visit).

Proportion of patients requiring any rescue medication: One RCT (Hale et al. 2010[9]) reported no significant between-group difference for proportion of patients requiring any rescue medication (96.2% OROS hydromorphone, 97.0%, placebo).

Total number of rescue medication tablets taken: One RCT (Hale et al. 2010[9]) stated the total number of rescue medication tablets taken was a secondary outcome; however, it did not report totals for either group.

Mean number of rescue medication tablets used daily: One RCT (Hale et al. 2010[9]) reported no significant between-group difference for mean number of rescue medication tablets used daily (0.8 OROS hydromorphone, 1.2 placebo, p=0.49). Hale et al. stated "Protocol restrictions provided a ceiling effect on the mean number of rescue medication tablets per day."

Incidence of TEAEs: One RCT (Vojtassak et al. 2011[8]) reported more moderate and severe TEAEs in the OROS hydromorphone group and similar rates of mild TEAEs between groups (Mild: 35% OROS hydromorphone, 30% placebo; Moderate: 33% OROS hydromorphone, 12% placebo; Severe 14% OROS hydromorphone, 4% placebo).

Incidence of serious TEAEs: One RCT (Vojtassak et al. 2011[8]) reported serious TEAEs more frequently in the placebo group (4.7% placebo, 2.9% OROS hydromorphone).

Drop-out rate due to AEs: Both RCTs (Vojtassak et al.,[8] Hale et al. 2010[9]) reported higher dropout rates with OROS hydromorphone (Vojtassak: 25.9% OROS hydromorphone, 4.7% placebo; Hale: 5.2% OROS hydromorphone, 2.2% placebo).

Incidence of AEs: One RCT (Hale et al. 2010[9]) reported a higher incidence of AEs in the placebo group (47.8% OROS hydromorphone, 54.5% placebo).

Incidence of serious AEs: One RCT (Hale et al. 2010[9]) reported serious AEs more frequently in the OROS hydromorphone group (4.5% OROS hydromorphone, 3.0% placebo).

Constipation: One RCT (Hale et al. 2010[9]) reported a higher incidence of constipation in the OROS hydromorphone group (7.5% OROS hydromorphone, 3.7% placebo).

Nausea: One RCT (Hale et al. 2010[9]) reported a higher incidence of nausea in the OROS hydromorphone group (9.0% OROS hydromorphone, 7.5% placebo).

Vomiting: One RCT (Hale et al. 2010[9]) reported a higher incidence of vomiting in the OROS hydromorphone group (6.0% OROS hydromorphone, 4.5% placebo).

Somnolence: One RCT (Hale et al. 2010[9]) reported a higher incidence of somnolence in the OROS hydromorphone group (0.7% OROS hydromorphone, 0% placebo).

Headache: One RCT (Hale et al. 2010[9]) reported a higher incidence of headache in the placebo group (5.2% OROS hydromorphone, 7.5% placebo).

Drug withdrawal syndrome: One RCT (Hale et al. 2010[9]) reported a higher incidence of drug withdrawal syndrome in the placebo group (9.7% OROS hydromorphone, 11.9% placebo).

Arthralgia: One RCT (Hale et al. 2010[9]) reported a higher incidence of arthralgia in the OROS hydromorphone group (6.0% OROS hydromorphone, 2.2% placebo).

Diarrhea: One RCT (Hale et al. 2010[9]) reported a higher incidence of diarrhea in the placebo group (3.7% OROS hydromorphone, 6.7% placebo).

Back pain: One RCT (Hale et al. 2010[9]) reported a higher incidence of back pain in the placebo group (4.5 % OROS hydromorphone, 6.0% placebo).

Insomnia: One RCT (Hale et al. 2010[9]) reported a higher incidence of insomnia in the OROS hydromorphone group (5.7% OROS hydromorphone, 3.7% placebo).

Oxycodone Extended Release Versus Placebo

Both RCTs[6,7] addressing this comparison reported on change in API and quality of life. Only one RCT[7] reported on response and function.

Pain (change in API): Both studies reported significant between groups differences (favoring oxycodone ER) for change in API at 12 weeks compared with baseline.[6,7]

Response (at least 50% improvement in PI): Katz et al. 2015[7] reported that significantly more patients in the Xtampza ER group had 50% improvement in pain intensity compared with placebo group (38.3% vs 24.5%, p=0.0032).

Response (at least 30% improvement in PI): Katz et al. 2015[7] reported that significantly more patients in the Xtampza ER group had 30% improvement in pain intensity compared with placebo group (49.2% vs 33.2%; p=0.0013).

PGIC: Katz et al. 2015[7] reported that significantly more Xtampza ER patients were "very much improved" (26.4% Xtampza ER, 14.3% placebo) and "improved" (40.4% Xtampza ER, 32.1% placebo) at the final visit; p<0.0001.

Quality of analgesia (overall for week 12): Friedmann et al. 2011[6] reported that Remoxy was rated significantly better than placebo at week 12 (last observation carried forward [LOCF]) in patient assessment of quality of analgesia (p=0.004).

Global assessment of study medication (overall for week 12): Remoxy was rated significantly better than placebo at week 12 (LOCF) in patient assessment of study medication(p=0.007) in one study.[6]

Quality of life (SF-12v2, physical component subscale): Both RCTs reported significant between group differences for the physical component score of the SF-12v2 favoring oxycodone ER.[6,7]

Quality of life (SF-12v2, mental component subscale): Results were mixed for this subscale as 1 study found a significant between group difference for the mental component score of the SF-12v2 favoring oxycodone ER[7] while the other study did not.[6]

WOMAC OA (3 subscales of pain, stiffness and physical function): Friedmann et al. 2011[6] reported WOMAC scores were numerically the same or better for Remoxy; significantly different for pain subscale only (p=0.023)

Function (RMDQ): At week 12, there was no significant difference in change of physical disability between groups measured by RMDQ (0.4±4.83 Xtampza ER, 0.7±5.32 placebo; p=0.4555).[7]

Gastrointestinal disorders: More Xtampza ER patients experienced GI disorders than placebo patients (24.4% Xtampza ER, 11.2% placebo) in one study.[7]

Nausea: Both RCTs reported that more oxycodone ER patients experienced nausea than placebo patients.[6,7]

Constipation: Both RCTs reported that more oxycodone ER patients experienced constipation than placebo patients.[6,7]

Dry mouth: More Remoxy patients experienced dry mouth than placebo patients (2% Remoxy, 0% placebo).[6]

Vomiting: More Remoxy patients experienced vomiting than placebo patients (14% Remoxy, 3% placebo).[6]

Diarrhea: Diarrhea occurred less in Remoxy patients than placebo patients (4% Remoxy, 6% placebo).[6]

Somnolence: More Remoxy patients experienced somnolence than placebo patients (11% Remoxy, 2% placebo).[6]

Dizziness: More Remoxy patients experienced dizziness than placebo patients (8% Remoxy, 4% placebo).[6]

Headache: No differences were reported for this outcome (5% in each arm).[6]

Pruritis: No differences were reported for this outcome (3% in each arm).[6]

Serious/Severe TEAEs**:** Each study reported 2 TEAEs occurred. Katz et al. 2015[7] reported 1 patient experienced gastroesophageal reflux and 1 patient experienced worsening erectile dysfunction. Friedmann et al. 2011[6] reported 1 patient each experienced orthostatic hypotension and fecaloma.

Discontinuation: Both RCs reported that fewer patients in the oxycodone group discontinued.

Tapentadol Extended Release Versus Placebo

3 studies (one systematic review,[1] two RCTs[2,3]) addressing this topic reported on several outcomes of interest.

Pain intensity (11-point NRS): All three studies[1-3] reported significant between group differences favoring tapentadol for higher reduction in pain intensity from baseline compared with placebo measured on an 11-point NRS.

Response (at least ≥50% pain reduction): All three studies[1-3] reported that tapentadol was associated with a statistically significant higher responder rate than placebo.

Response (at least ≥30% pain reduction): Both RCTs[2,3] reported that tapentadol was associated with a statistically significant higher responder rate than placebo.

Patient global impression of change (PGIC): All three studies[1-3] reported tapentadol treated patients were more likely to consider themselves "much improved" or "very much improved" compared with placebo.

Quality of life (SF-36 physical component summary score): The Santos review[1] and one RCT (Vinik et al. 2014[3]) reported that tapentadol was associated with a statistically significant higher increase in SF-36 physical component summary score (Santos: Mean Difference 2.57 (95% CI: 1.69 to 3.44; I^2=0%; Vinik: Least squares mean difference 2.1 (95% CI: 0.67 to 3.57; p=0.004)).

Quality of life (SF-36 role-physical and bodily pain subscales): One RCT (Vinik et al. 2014[3]) reported significant between group differences (favoring tapentadol) for these subscales ($p \leq 0.004$).

Quality of life (EQ-5D): Results were mixed for this outcome. One study[3] reported significant between group differences (favoring tapentadol) (least squares mean difference 0.10 (95% CI 0.05 to -0.15; $p<0.001$), while one review (2 studies) reported no significant differences between groups.[1]

Quality of life (WOMAC): One review (2 studies, 1313 patients) reported no significant differences between groups.

Quality of life (BPI-SF): One RCT[3] reported significant between group differences (favoring tapentadol) for mean pain interference scores (p=0.003) and mean pain intensity subscale scores ($p<0.001$).

Quality of life (NPSI): One RCT[3] reported significant between group differences (favoring tapentadol) for NPSI subscales and total score ($p \leq 0.015$ for all scores).

Incidence of TEAEs: Both RCTs[2,3] reported TEAE incidence was higher with Tapentadol.

Treatment-emergent serious adverse events: Both RCTs[2,3] reported that rates were higher with tapentadol.

Discontinuation due to treatment-emergent adverse effects (TEAEs): Results were mixed for this outcome. In one review (3 studies), Tapentadol was associated with a significantly higher risk of withdrawal due to adverse effects compared with placebo (RR 2.68 (95% CI: 2.05 to 3.52; I^2=0%; NNTH 10; 95% CI 7 to 12, for 12 weeks).[1] 2 RCTs however reported a non-significant higher risk of discontinuation due to TEAEs with Tapentadol.[2,3]

Serious adverse effects: Evidence from one review (3 studies) indicated no differences in incidence of serious adverse effects (RR 1.01 (95% CI: 0.47 to 2.16; I^2=21%).

Adverse effects: Evidence from one review (2 studies, 1318 patients)[1] indicated that significantly more participants treated with Tapentadol had a higher risk of overall incidence (RR 1.25 (95% CI: 1.16 to 1.35; I^2=0%).

Constipation: One review (3 studies, 1974 patients)[1] reported a higher risk of constipation with Tapentadol (RR 2.43 (95% CI: 1.86 to 3.17; I^2=4%).

Nausea: One review (3 studies, 1974 patients)[1] reported a higher risk with Tapentadol (RR 2.81 (95% CI: 2.18 to 3.62; I^2=0%).

Vomiting: One review (3 studies, 1974 patients)[1] reported a higher risk with Tapentadol (RR 2.77 (95% CI: 1.83 to 4.21; I^2=56%).

Dry mouth: One review (3 studies, 1974 patients)[1] reported a higher risk with tapentadol (RR 3.08 (95% CI 1.92 to 4.94; I^2=0%).

Somnolence: One review (3 studies, 1974 patients)[1] reported a higher risk with tapentadol (RR 3.27 (95% CI 2.26 to 4.73; I^2=19%)

Dizziness: One review (3 studies, 1974 patients)[1] reported a higher risk with tapentadol (RR 2.73 (95% CI 2.08 to 3.60; I^2=13%).

Fatigue: One review (3 studies, 1974 patients)[1] reported a higher risk with tapentadol (RR 2.15 (95% CI: 1.48 to 3.11; I^2=0%).

Diarrhea: One review (3 studies, 1974 patients)[1] reported no differences between groups for this outcome (RR 0.85 (95% CI: 0.59 to 1.23; I^2=0%).

Headache: One review (3 studies, 1974 patients)[1] reported no differences between groups for this outcome (RR 1.13 (95% CI: 0.91 to 1.40; I^2=44%).

Pruritis: One review (3 studies, 1974 patients)[1] reported no differences between groups for this outcome (RR 2.67 (95% CI: 0.85 to 8.37; I^2=72%).

Discontinuation due to adverse events: One RCT (Schwartz et al. 2014[2]) reported rates of discontinuation due to adverse events were higher with tapentadol (7.8% placebo, 14.8% tapentadol).

Withdrawal: One RCT (Schwartz et al. 2014[2]) reported that rates for "no opioid withdrawal" were slightly higher with placebo for patients with COWS assessment who did not discontinue during the first week of the double-blind phase, and did not take opioids after discontinuation (90.5% tapentadol, 96.7% placebo).

Studies Addressing Short-term Safety

Buprenorphine Transdermal Delivery System Versus Placebo

One 8-week RCT (Gordon et al. 2010[16]) is included for this comparison.

Incidence of AEs: Significantly more patients reported AEs in the BTDS group (89.0%) than the placebo group (64.7%, p=0.003).

Nausea: Significantly more patients reported nausea in the BTDS group (p<0.001).

Vomiting: Significantly more patients reported vomiting in the BTDS group (p=0.008).

Somnolence: Significantly more patients reported somnolence in the BTDS group (p=0.020).

Dry mouth: Significantly more patients reported dry mouth in the BTDS group (p=0.003).

Dizziness: Significantly more patients reported dizziness in the BTDS group (p<0.001).

Drop-out rate due to AEs: More patients dropped out due to AEs in the BTDS group (21.6%) than the placebo group (4.4%).

Incidence of serious AEs: No serious AEs were reported.

Loss to follow-up: Similar patients were lost to follow-up (1.4% BTDS, 1.5% placebo).

Controlled Release Oxycodone/Controlled Release Naloxone Versus Placebo

One 8-week RCT (Cloutier et al. 2013[18]) is included for this comparison.

Incidence of AEs: No significant between-group difference was reported (p=0.0679).

Somnolence: Significantly more patients in the CR oxycodone/CR naloxone group reported somnolence (p=0.0455).

Drop-out rate due to AEs: More patients dropped out due to AEs in the CR oxycodone/CR naloxone group (7.2%) than placebo (6.0%).

Incidence of serious AEs: Similar incidence (4.8%) was reported.

Loss to follow-up: Fewer patients were lost to follow-up in the CR oxycodone/CR naloxone group (0%) than the placebo group (2.6%).

Tramadol Extended Release Versus Placebo

Three short-term RCTs (Schiphorst Preuper et al. 2014,[13] Hyup Lee et al. 2013,[14] and Uberall et al. 2012[15] addressed this comparison.

Incidence of TEAEs: One RCT (Uberall et al. 2012[15]) reported incidence of TEAEs were significantly higher (p=0.001) in patients treated with tramadol ER (34.5%) than placebo (15.8%).

Time until TEAEs: One RCT (Uberall et al. 2012[15]) reported time until TEAEs was significantly shorter (p=0.001) in patients treated with tramadol ER.

Incidence of serious TEAEs: One RCT (Uberall et al. 2012[15]) reported no serious TEAEs in any group and no deaths occurred during the study.

Drop-out rate due to TEAEs: One RCT (Uberall et al. 2012[15]) reported significantly more patients dropped out due to TEAEs in the tramadol ER group (p=0.014).

Loss to follow-up: One RCT (Schiphorst Preuper et al. 2014[13]) reported 4% of patients in the tramadol ER group were lost to follow-up due to family circumstances.

Incidence of AEs: Two RCTs (Schiphorst Preuper et al. 2014,[13] Hyup Lee et al. 2013[14]) reported more AEs in the tramadol ER group (Schiphorst Preuper: 50% tramadol ER, 24% placebo; Hyup Lee: 83.2% tramadol ER, 54.2% placebo).

Incidence of serious AEs: One RCT (Hyup Lee et al. 2013[14]) reported a serious AE (unrelated to study drug) in 1 patient in the tramadol ER group. No deaths occurred during the study.

Drop-out rate due to AEs: Two RCTs (Schiphorst Preuper et al. 2014,[13] Hyup Lee et al. 2013[14]) reported higher drop-out rates due to AEs in the tramadol ER group (Schiphorst Preuper: 8% tramadol ER, 0% placebo; Hyup Lee: 19.2% tramadol ER, 5.0% placebo).

Nausea: Two RCTs (Hyup Lee et al. 2013,[14] Uberall et al. 2012[15]) reported a higher incidence of nausea in the tramadol ER group (Hyup Lee: 36.8% tramadol ER, 10.0% placebo; Überall: 19.0% tramadol ER, 2.5% placebo; p=0.001)

Vomiting: One RCT (Uberall et al. 2012[15]) reported significantly more vomiting in the tramadol ER group (11.2% tramadol ER, 0.8% placebo; p<0.001).

Dizziness: Two RCTs (Hyup Lee et al. 2013,[14] Uberall et al. 2012[15]) reported a higher incidence of dizziness in the tramadol ER group (Hyup Lee: 28.0% tramadol ER, 8.3% placebo; Überall: 12.9% tramadol ER, 3.3% placebo; p=0.008).

Fatigue: One RCT (Uberall et al. 2012[15]) reported no significant between-group differences.

Headache: One RCT (Hyup Lee et al. 2013[14]) reported a higher incidence of headache in the tramadol ER group (8.8%) than the placebo group (5.0%).

Dyspepsia: One RCT (Hyup Lee et al. 2013[14]) reported similar incidence (~10%).

Tramadol Extended Release Versus Flupirtine

One short-term RCT (Uberall et al. 2012[15]) reported on this comparison, and we reported only safety-related outcomes. The outcomes in the tramadol ER group are the same here as above when compared to placebo. They are duplicated for convenience.

Incidence of TEAEs: Significantly more patients experienced TEAEs in the tramadol ER group (34.5%) than the flupirtine group (21.0%, p=0.039).

Time until TEAEs: Patients experienced TEAEs significantly sooner in the tramadol ER group (p<0.001).

Incidence of serious TEAEs: No serious TEAEs were reported in either group. No deaths occurred during the study.

Drop-out rate due to TEAEs: Significantly more patients dropped out due to TEAEs in the tramadol ER group (12.1%) than the flupirtine group (3.4%, p=0.017).

Nausea: Significantly more patients reported nausea in the tramadol ER group (19.0%) than the flupirtine group (1.7%, p<0.001).

Vomiting: Significantly more patients group reported vomiting in the tramadol ER (11.2%) than the flupirtine group (0%, p<0.001).

Dizziness: More patients reported dizziness in the tramadol ER group (12.9%) than the flupirtine group (6.0%, p-value not significant).

Fatigue: No significant between group differences were reported for fatigue.

Tramadol Versus Placebo

One short-term RCT (Norrbrink and Lundeberg 2009[17]) addressed this comparison, and we reported only safety-related outcomes.

Incidence of AEs: Significantly more patients reported 1 or more AEs in the tramadol group (91%) than the placebo group (58%, p=0.02).

Drop-out rate due to AEs: More patients dropped out due to AEs in the tramadol group (52.2%) than in the placebo group (8.3%).

Tiredness: More patients reported tiredness in the tramadol group (74%) than the placebo group (17%).

Dry mouth: More patients reported dry mouth in the tramadol group (52%) than the placebo group (25%).

Dizziness: More patients reported dizziness in the tramadol group (52%) than the placebo group (25%).

Sweating: More patients reported sweating in the tramadol group (39%) than the placebo group (25%).

Constipation: More patients reported constipation in the tramadol group (35%) than the placebo group (33%).

Nausea: More patients reported nausea in the tramadol group (39%) than the placebo group (25%).

Overall Quality of Evidence Rating

The overall quality of the evidence was assessed for each outcome using the GRADE system, which assigns a rating of High, Moderate, Low or Very low. By default, RCTs start at High quality of evidence and observational intervention studies start at Low quality of evidence. The evidence is then assessed for potential deficiencies in four primary domains: overall study quality (usually the average or median quality of individual studies for each outcome), indirectness (of interventions, study populations, outcomes, and/or comparisons), inconsistency (in direction and/or magnitude of effect) and imprecision (uncertainty in the estimate of effect due to variance or low sample size). Deficiencies in any of these domains may result in downgrading the quality of evidence by one or two levels.

Two RCTs[11,12] evaluating long-term use of BTDS versus placebo found moderate quality of evidence for pain intensity due to serious limitations (mostly due to attrition). Low quality evidence indicating no significant differences in all remaining pain- and function-related outcomes for patients receiving BTDS or placebo. The low quality rating was due to limitations in the methodological quality of the included studies and imprecision (only 1 small single study reporting each outcome and lack of reporting measures of dispersion). The studies suggested BTDS improved pain control but with substantial adverse events.[11,12] One RCT with a short-term follow-up[16] found low quality evidence for safety-related outcomes of BTDS due to serious study limitations (mostly attrition) and serious imprecision (small single study).

One RCT[10] evaluating long-term use of FBT versus placebo found low quality of evidence indicating statistically significant differences for 4 outcomes measuring relief of BTP episodes. The low quality rating was due to limitations in the methodological quality of the study and reporting of these outcomes by one small study.

Two RCTs[4,5] evaluating long-term use of hydrocodone ER versus placebo found very low quality of evidence indicating mixed results for reductions in pain intensity. The very low quality rating was due to limitations in the methodological quality of the studies, inconsistent results, and lack of reporting measures of dispersion. Both RCTs found low quality of evidence indicating significant differences for response but no significant differences for function and quality-of-life measures. The low quality rating was due to limitations in the methodological quality of the studies, one single study reporting each outcome, and lack of reporting measures of dispersion.

Two RCTs[8,9] evaluating long-term use of OROS hydromorphone versus placebo found low quality of evidence indicating mixed results for primary efficacy pain outcomes. The low quality rating was due to

limitations in the methodological quality of the studies and imprecision (most outcomes were reported by only 1 study and studies did not report measures of dispersion).

One RCT addressing short-term safety for CR oxycodone/CR naloxone versus placebo[18] found moderate quality of evidence indicating no significant between-group difference for overall incidence of AEs and incidence of serious AEs. This rating was due to reporting from one single study and lack of reporting measures of dispersion.

Two RCTs[6,7] evaluating long-term use of Oxycodone ER versus placebo found low quality of evidence indicating significant between-group differences for change in API[6,7] and responders[7] The low quality rating was due to study limitations (high attrition in both studies, lack of reporting randomization and allocation methods in 1 study[6]) and imprecision (mostly due to not reporting measures of dispersion).

Three studies[1-3] evaluating long-term use of Tapentadol ER versus placebo found low quality evidence indicating significant between-groups differences for pain reduction and responders. This low quality rating was due to limitations in the methodological quality of the studies (reporting of outcomes in include studies in the review,[1] high attrition in 2 RCTs[2,3]) and imprecision (including wide confidence intervals). Most outcomes received a low quality rating of the evidence for similar reasons.

Three RCTs addressing short-term safety of tramadol ER versus placebo[13-15] found moderate-to-low quality of evidence for AE-related outcomes. One RCT addressing short-term safety for tramadol ER versus flupirtine[15] found low quality of evidence indicating significant between-group differences for incidence of TEAEs and drop-out rates. This low quality rating was due to only one study reporting on this comparison and serious limitations in study quality. Lastly, one RCT addressing short-term safety of tramadol versus placebo[17] found very low quality of evidence for AE-related outcomes. This very low rating was due to high attrition and follow-up rate greatly varying between groups. Additionally, patients with paraplegia and tetraplegia were not evenly distributed between treatment groups—more patients with paraplegia than tetraplegia were randomly assigned to the placebo group. Patients were allowed to continue previously stable doses of opioids during the study, which also may have confounded outcomes. Table 1-a and Table 1-b present the overall ratings for the outcomes reported on in the studies included as evidence for this key question.

Table 1-a. Overall Assessment of Quality of Evidence Base (Long-term Effectiveness and Safety)

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Buprenorphine Transdermal Delivery System Versus Placebo								
Pain Intensity (NRS-11 score)	2 RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12])	BTDS (5, 10, or 20 µg/h;[11] 10 or 20 µg/h[12]) vs. placebo (740 patients)	Both studies reported significantly greater reductions in pain intensity with BTDS. Breivik: Difference between means -0.5 (95% CI: -0.95 to -0.05; p=0.0292) Steiner: Difference between means -0.58 (95% CI: -1.02 to -0.14; p=0.0104)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
WOMAC OA pain subscale	1 RCT (Breivik et al. 2010[11])	BTDS (5, 10, or 20 µg/h) vs. placebo (199 patients)	No significant between-group difference reported for pain. Difference -0.86 (95% CI: -1.76 to 0.04; p=0.061)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study	Low
WOMAC OA stiffness subscale	1 RCT (Breivik et al. 2010[11])	BTDS (5, 10, or 20 µg/h) vs. placebo (199 patients)	No significant between-group difference reported for stiffness. Difference -0.18 (95% CI: -0.56 to 0.19; p=0.331)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study	Low
WOMAC OA functional ability subscale	1 RCT (Breivik et al. 2010[11])	BTDS (5, 10, or 20 µg/h) vs. placebo (199 patients)	No significant between-group difference reported for functional ability. Difference -2.90 (95% CI: -5.86 to 0.06; p=0.055)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
WOMAC OA overall score	1 RCT (Breivik et al. 2010[11])	BTDS (5, 10, or 20 µg/h) vs. placebo (199 patients)	No significant between-group difference reported for overall pain scores. Difference -3.95 (95% CI: -8.06 to 0.16; p=0.0592)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study	Low
Daily Rescue Medication Use	2 RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12])	BTDS (5, 10, or 20 µg/h;[11] 10 or 20 µg/h[12]) vs. placebo (740 patients)	Both studies reported no significant between-group differences. Breivik: Mean of 2 tablets of 0.5 g paracetamol per day for all patients Steiner: Difference -0.124 (95% CI: -0.296 to 0.048; p=0.1586)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One study did not report measures of dispersion[11]	Low
Number of Nights Woken Because of Pain	1 RCT (Breivik et al. 2010[11])	BTDS (5, 10, or 20 µg/h) vs. placebo (199 patients)	No significant between-group difference was reported (p=0.8542).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Quality of Sleep (5-point scale)	1 RCT (Breivik et al. 2010[11])	BTDS (5, 10, or 20 µg/h) vs. placebo (199 patients)	No significant between-group difference was reported.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Sleep Disturbance (subscale MOS Sleep Scale)	1 RCT (Steiner et al. 2011[12])	BTDS (10 or 20 µg/h) vs. placebo (541 patients)	Significantly less sleep disturbance was reported with BTDS. Difference -4.4 (95% CI: -7.5 to -1.3; p=0.0062)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study	Low
PGIC	1 RCT (Breivik et al. 2010[11])	BTDS (5, 10, or 20 µg/h) vs. placebo (199 patients)	A significantly greater improvement in PGIC was reported with BTDS (p=0.0171).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Time Until Completion of Study or Withdrawal	1 RCT (Breivik et al. 2010[11])	BTDS (5, 10, or 20 µg/h) vs. placebo (199 patients)	Patients withdrew from treatment earlier with BTDS. 157 days BTDS (164 for hip, 143 for knee); 167 days placebo (almost identical for hip and knee)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Incidence of AEs	1 RCT (Breivik et al. 2010[11])	BTDS (5, 10, or 20 µg/h) vs. placebo (199 patients)	More patients in the BTDS group reported AEs. 92.0% BTDS, 73.7% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Constipation	2 RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12])	BTDS (5, 10, or 20 µg/h;[11] 10 or 20 µg/h[12]) vs. placebo (738 patients)	Both studies reported more constipation with BTDS. Breivik: 24.0% BTDS, 5.1% placebo Steiner: 4% BTDS, 1% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for both studies[11,12]	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Nausea	2 RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12])	BTDS (5, 10, or 20 µg/h;[11] 10 or 20 µg/h[12]) vs. placebo (738 patients)	Both studies reported more nausea with BTDS. Breivik: 37.0% BTDS, 10.0% placebo Steiner: 13% BTDS, 11% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for both studies[11,12]	Low
Vomiting	2 RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12])	BTDS (5, 10, or 20 µg/h;[11] 10 or 20 µg/h[12]) vs. placebo (738 patients)	Both studies reported more vomiting with BTDS. Breivik: 16.0% BTDS, 2.0% placebo Steiner: 4% BTDS, 2% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for both studies[11,12]	Low
Dizziness	2 RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12])	BTDS (5, 10, or 20 µg/h;[11] 10 or 20 µg/h[12]) vs. placebo (738 patients)	Both studies reported more dizziness with BTDS. Breivik: 25.0% BTDS, 9.1% placebo Steiner: 4% BTDS, 1% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for both studies[11,12]	Low
Headache	2 RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12])	BTDS (5, 10, or 20 µg/h;[11] 10 or 20 µg/h[12]) vs. placebo (738 patients)	One study reported more headache with BTDS. Breivik: 7.0% BTDS, 6.1% placebo One study reported no difference between groups. Steiner: 5% BTDS, 5% placebo	Serious limitations (-1)	Serious inconsistency (-1)	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for both studies[11,12]	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Drop-out Rate Due to AEs	2 RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12])	BTDS (5, 10, or 20 µg/h;[11] 10 or 20 µg/h[12]) vs. placebo (738 patients)	More patients in the BTDS group dropped out due to AEs. Breivik: 31% BTDS, 2% placebo Steiner: 16% BTDS, 7% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for both studies[11,12]	Low
Incidence of Serious AEs	2 RCTs (Breivik et al. 2010,[11] Steiner et al. 2011[12])	BTDS (5, 10, or 20 µg/h;[11] 10 or 20 µg/h[12]) vs. placebo (738 patients)	Both studies reported a similar incidence of serious AEs with BTDS. Breivik: 5% BTDS, 4% placebo Steiner: 1.1% BTDS, 0.7% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for both studies[11,12]	Low
Incidence of TEAEs	1 RCT (Steiner et al. 2011[12])	BTDS (10 or 20 µg/h) vs. placebo (539 patients)	55% BTDS, 52% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study	Low
Loss to Follow-up	1 RCT (Steiner et al. 2011[12])	BTDS (10 or 20 µg/h) vs. placebo (541 patients)	1 patient in the BTDS group was lost to follow-up during the double-blind phase	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Fentanyl Buccal Tablets Versus Placebo								
Pain ($SPID_{60}$)	1 RCT (Farrar et al. 2010[10])	Fentanyl buccal tablets (FBT) – 100 µg to 800 µg/day vs. placebo (79 patients)	Significantly greater for BTP episodes treated with FBT compared with placebo after week 12 (mean±SD 7.7±6.2 FBT, 4.6±4.7 placebo; p<0.001). Similar findings were demonstrated (after week 12) 30 minutes after drug administration (2.8±2.8 FBT, 1.6±2.0; p<0.01), 90 minutes after drug administration (12.9±9.6 FBT, 7.5±7.5 placebo; p≤0.001), and 120 minutes after administration (18.2±13.1 FBT, 10.4±10.3 placebo; p≤0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study	Low
Pain (>33% improvement)	1 RCT (Farrar et al. 2010[10])	FBT (100 µg to 800 µg/day) vs. placebo (79 patients)	The proportion of BTP episodes with ≥33% improvement in PI was greater after FBT compared with placebo, beginning at 5 minutes post dose (7% FBT, 3% placebo; p=0.0150) and increasing to a maximum of 90 minutes (54% FBT, 31% placebo; p<0.0001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Pain (>50% improvement)	1 RCT (Farrar et al. 2010[10])	FBT (100 µg to 800 µg/day) vs. placebo (79 patients)	The proportion of BTP episodes with ≥50% improvement in PI reached statistical significance at 15 minutes post dose with FBT compared with placebo (17% vs 10%; p=0.0216) and was maintained at all subsequent time points.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion	Low
Pain relief (PR)	1 RCT (Farrar et al. 2010[10])	FBT (100 µg to 800 µg/day) vs. placebo (79 patients)	The average onset of PR began at 5 minutes (12% FBT, 7% placebo; p=0.0175), with meaningful PR by ≤10 minutes (14% FBT, 7% placebo; p=0.0006).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion	Low
Supplemental medication	1 RCT (Farrar et al. 2010[10])	FBT (100 µg to 800 µg/day) vs. placebo (79 patients)	Supplemental medication was used in fewer BTP episodes treated with FBT-treated compared with placebo-treated episodes (26% FBT, 40% placebo treated; odds ratio (OR) 1.8640 (95% CI: 1.3 to 2.7; p=0.0007).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Hydrocodone Extended Release Versus Placebo								
Pain intensity (11-point NRS)	2 RCTs (Hale et al. 2015,[4] Rauck et al. 2014[5])	Hydrocodone ER vs. placebo (594 patients) Hale: 30 mg to 180 mg/day Rauck: 40 mg to 200 mg/day	One RCT reported significant between-group differences favoring hydrocodone for higher reduction in pain intensity compared with placebo at day 85[5] while the other study reported no significant difference (p=0.134) for mean change in API at week 12.[4] Post hoc analysis in this study[4] did indicate that the change in weekly API was significantly lower with hydrocodone ER when excluding the lowest dose (15 mg); LSM -0.20 vs. 0.40; p=0.032.	Serious limitations (-1)	Serious inconsistency (-1)	No serious indirectness	Serious imprecision (-1) Neither study reported measures of dispersion	Very low
Response (≥50% average PI score improvement)	1 RCT (Rauck et al. 2014[5])	Hydrocodone ER (40 mg to 200 mg/day) vs. placebo (294 patients)	Significantly more responders were demonstrated in the HC-ER group at day 85 (48% HC-ER, 23% placebo; p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Response (≥30% average PI score improvement)	1 RCT (Rauck et al. 2014[5])	Hydrocodone ER (40 mg to 200 mg/day) vs. placebo (294 patients)	Significantly more responders were demonstrated in the HC-ER group at day 85 (68% HC-ER, 31% placebo; p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Response (50% increases from baseline in weekly API)	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	Significantly more patients receiving placebo had >50% increase in weekly API at week 8 (18% vs. 6%; p=0.005) and week 12 (15% vs. 6%; p=0.041).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Response (33% increases from baseline in weekly API)	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	Significantly more patients receiving placebo had >33% increase in weekly API at week 2 (22% vs. 11%; p=0.016) and week 12 (24% vs. 11%; p=0.017).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Worst Pain Intensity	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	Mean weekly WPI was significantly lower with hydrocodone ER at week 2 (0.27 vs. -0.15; p=0.025), week 8 (0.00 vs. -0.68; p=0.004) and week 12 (-0.03 vs. -0.60; p=0.025).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Function (PAF)	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	No significant differences were reported between hydrocodone ER and placebo.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Function (CAPF)	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	No significant differences were reported between hydrocodone ER and placebo.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Symptom severity (CGI-S)	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	No significant differences were reported between hydrocodone ER and placebo.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Pain (BPI-SF)	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	No significant differences were reported between hydrocodone ER and placebo.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Quality of life (SF-36)	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	No significant differences were reported between hydrocodone ER and placebo.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Satisfaction (SGAM)	1 RCT (Rauck et al. 2014[5])	Hydrocodone ER (40 mg to 200 mg/day) vs. placebo (294 patients)	Significantly more HC-ER patients were satisfied with pain medication at day 85 compared with placebo patients (0.8±1.3 HC-ER, 0.0±1.4 placebo; p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) One single study	Low
Incidence of TEAEs (treatment phase)	1 RCT (Rauck et al. 2014[5])	Hydrocodone ER (40 mg to 200 mg/day) vs. placebo (294 patients)	Significantly more HC-ER patients experienced at least 1 TEAE (60% HC-ER, 44% placebo; p=0.006).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Discontinuation due to TEAEs	1 RCT (Rauck et al. 2014[5])	Hydrocodone ER (40 mg to 200 mg/day) vs. placebo (294 patients)	More patients receiving placebo discontinued due to TEAEs than receiving HC-ER (9 placebo (4 from withdrawal), 2 HC-ER).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Constipation	1 RCT (Rauck et al. 2014[5])	Hydrocodone ER (40 mg to 200 mg/day) vs. placebo (294 patients)	Significantly more HC-ER patients experienced constipation (7.9% HC-ER, 0% placebo; p<0.001)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Discontinuation due to AEs (maintenance phase)	2 RCTs (Hale et al. 2015,[4] Rauck et al. 2014[5])	Hydrocodone ER vs. placebo (594 patients) Hale: 30 mg to 180 mg/day Rauck: 40 mg to 200 mg/day	Rates were higher with hydrocodone ER in one study and lower in another study. Hale: 9 hydrocodone ER, 3 placebo Rauck: 1.3% HC-ER, 3.3% placebo	Serious limitations (-1)	Serious inconsistency (-1)	No serious indirectness	No serious imprecision (-1) No measures of dispersion reported	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Withdrawal	2 RCTs (Hale et al. 2015,[4] Rauck et al. 2014[5])	Hydrocodone ER vs. placebo (594 patients) Hale: 30 mg to 180 mg/day Rauck: 40 mg to 200 mg/day	One study reported significantly more placebo patients experienced withdrawal syndrome (0.7% HC-ER, 6% placebo; p<0.019) while the other study reported similar withdrawal.[4] Mean SOWS scores, mean COWS scores and proportion of patients in each category of withdrawal symptoms (normal, mild, moderate, moderately severe, or severe withdrawal) were similar between groups at each visit.[4]	Serious limitations (-1)	Serious inconsistency (-1)	No serious indirectness	No serious imprecision (-1) No measures of dispersion	Very low
Aberrant drug-related behaviors	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	Positive results for aberrant drug-use behaviors (start of open label): 15 hydrocodone ER, 7 placebo Low risk for aberrant use behavior (week 2): 71% hydrocodone ER, 78% placebo No indication of aberrant drug-use behavior (endpoint): 100 hydrocodone ER, 110 placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Inappropriate opioid use behaviors	1 RCT (Hale et al. 2015[4])	Hydrocodone ER (30 mg to 180 mg/day) vs. placebo (302 patients)	Positive results for inappropriate opioid use behavior (start of open label): 2 hydrocodone ER, 1 placebo No indication of inappropriate opioid use (endpoint): 101 hydrocodone, 111 placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Loss to follow-up	1 RCT (Rauck et al. 2014[5])	Hydrocodone ER (40 mg to 200 mg/day) vs. placebo (294 patients)	Rates were higher with HC-ER patients (0.7% HC-ER, 0% placebo)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
OROS Hydromorphone Versus Placebo								
Pain (10-point BPI)	1 RCT (Vojtassak et al. 2011[8])	OROS hydromorphone (4, 8, 12, 16, 24, or 32 mg daily) vs. placebo (288 patients)	No significant between-group difference was reported. Difference -0.2365 (95% CI –0.5357 to 0.0627; p=0.1212).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, 95% CI includes the possibility of no difference	Low
Pain (10-point BPI subscales “pain at its worst in the last 24 h”, “pain at its least in the last 24 h”, and “pain right now”)	1 RCT (Vojtassak et al. 2011[8])	OROS hydromorphone (4, 8, 12, 16, 24, or 32 mg daily) vs. placebo (288 patients)	No significant between-group differences were reported for these BPI subscales.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Pain (11-point NRS patient diary score)	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (266 patients)	A significantly larger increase in pain intensity occurred in the placebo group (p<0.001). 0.2 units OROS hydromorphone, 1.6 units placebo.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Pain intensity (weighted mean NRS diary score)	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (266 patients)	A significantly larger increase in pain intensity occurred in the placebo group (p<0.001). 0.4 units OROS hydromorphone, 1.2 units placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Pain (weekly 11-point NRS office scores)	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (266 patients)	A significantly greater improvement in weekly pain scores recorded in office were reported for the OROS hydromorphone group (p<0.05) for every week except week 3.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Time to treatment failure	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (266 patients)	A significant between-group difference was reported for time to discontinuation due to treatment failure, with failure occurring sooner in the placebo group than the OROS hydromorphone group (p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Quality of life (WOMAC OA index)	1 RCT (Vojtassak et al. 2011[8])	OROS hydromorphone (4, 8, 12, 16, 24, or 32 mg daily) vs. placebo (288 patients)	No significant between-group difference was reported.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Quality of life (WOMAC OA pain subscale)	1 RCT (Vojtassak et al. 2011[8])	OROS hydromorphone (4, 8, 12, 16, 24, or 32 mg daily) vs. placebo (288 patients)	No significant between-group difference was reported.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Quality of life (SF-36 pain subscale)	1 RCT (Vojtassak et al. 2011[8])	OROS hydromorphone (4, 8, 12, 16, 24, or 32 mg daily) vs. placebo (288 patients)	No significant between-group difference was reported.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
HRQoL	1 RCT (Vojtassak et al. 2011[8])	OROS hydromorphone (4, 8, 12, 16, 24, or 32 mg daily) vs. placebo (288 patients)	No significant between-group difference was reported.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
PGA (5-point scale)	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (266 patients)	A significant between-group difference was reported favoring OROS hydromorphone over placebo ($p<0.001$).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
RMDQ	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (266 patients)	Significant between-group differences were reported favoring OROS hydromorphone over placebo ($p<0.05$) for mean weekly changes from baseline in RMDQ scores for weeks 1, 2, 3, 8, and 12 (or final visit). No significant between-group differences were reported for mean weekly changes from baseline in RMDQ scores for weeks 4, 6, or 10. A significant between-group difference was reported favoring OROS hydromorphone over placebo ($p<0.005$) for median change of RMDQ scores from baseline to week 12 (or final visit).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Proportion of patients requiring any rescue medication	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (266 patients)	No significant between-group difference was reported for proportion of patients requiring any rescue medication. 96.2% OROS hydromorphone, 97.0%, placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Total number of rescue medication tablets taken	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (266 patients)	The total number of rescue medication tablets taken was not reported for either group.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Mean number of rescue medication tablets used daily	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (266 patients)	No significant between-group difference was reported for mean number of rescue medication tablets used daily (OROS hydromorphone 0.8, placebo 1.2, p=0.49). According to the protocol, patients were limited to 2 tablets of rescue medication per day after week 2 of the study.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Incidence of TEAEs	1 RCT (Vojtassak et al. 2011[8])	OROS hydromorphone (4, 8, 12, 16, 24, or 32 mg daily) vs. placebo (288 patients)	More moderate and severe TEAEs were reported in the OROS hydromorphone group and similar rates of mild TEAEs were reported between groups. Mild: 35% OROS hydromorphone, 30% placebo Moderate: 33% OROS hydromorphone, 12% placebo Severe: 14% OROS hydromorphone, 4% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Incidence of serious TEAEs	1 RCT (Vojtassak et al. 2011[8])	OROS hydromorphone (4, 8, 12, 16, 24, or 32 mg daily) vs. placebo (288 patients)	Serious TEAEs were reported more frequently in the placebo group. Vojtassak: 4.7% placebo, 2.9% OROS hydromorphone	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Dropout rate due to AEs	2 RCTs (Vojtassak et al. 2011[8] Hale et al. 2010[9])	OROS hydromorphone (4, 8, 12, 16, 24, or 32 mg daily;[8] ≥12 mg and ≤64 mg daily[9]) vs. placebo (556 patients)	Both studies reported higher dropout rates with OROS hydromorphone. Vojtassak: 25.9% OROS hydromorphone, 4.7% placebo Hale: 5.2% OROS hydromorphone, 2.2% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported in 2 studies[8,9]	Low
Incidence of AEs	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of AEs was reported in the placebo group. 47.8% OROS hydromorphone, 54.5% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Incidence of serious AEs	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	Serious AEs were reported more frequently in the OROS hydromorphone group. 4.5% OROS hydromorphone, 3.0% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Constipation	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of constipation was reported in the OROS hydromorphone group. 7.5% OROS hydromorphone, 3.7% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Nausea	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of nausea was reported in the OROS hydromorphone group. 9.0% OROS hydromorphone, 7.5% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Vomiting	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of vomiting was reported in the OROS hydromorphone group. 6.0% OROS hydromorphone, 4.5% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Somnolence	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of somnolence was reported in the OROS hydromorphone group. 0.7% OROS hydromorphone, 0% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Headache	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of headache was reported in the placebo group. 5.2% OROS hydromorphone, 7.5% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Drug Withdrawal Syndrome	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of drug withdrawal syndrome was reported in the placebo group. 9.7% OROS hydromorphone, 11.9% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Arthralgia	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of arthralgia was reported in the OROS hydromorphone group. 6.0% OROS hydromorphone, 2.2% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Diarrhea	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of diarrhea was reported in the placebo group. 3.7% OROS hydromorphone, 6.7% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Back Pain	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of back pain was reported in the placebo group. 4.5 % OROS hydromorphone, 6.0% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Insomnia	1 RCT (Hale et al. 2010[9])	OROS hydromorphone (≥12 mg and ≤64 mg daily) vs. placebo (268 patients)	A higher incidence of insomnia was reported in the OROS hydromorphone group. 5.7% OROS hydromorphone, 3.7% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Oxycodone Extended Release Versus Placebo								
Pain (API)	2 RCTs (Katz et al. 2015[7] and Friedmann et al. 2011[6])	Oxycodone extended release (ER) vs. placebo (801 patients) Katz: 40 to 160 mg/day Friedmann: 10 to 80 mg/day	Significant between groups differences (favoring oxycodone ER) were demonstrated for change in API at 12 weeks compared with baseline. Katz: mean difference -1.56±0.27 (95% CI: -2.1 to -1.1; p<0.0001). Friedmann: Mean area under the curve (AUC) for the change in PI scores was significantly greater for Remoxy (-54.9 Remoxy, -30.4 placebo; p=0.007)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion in one study[6]	Low
Response (at least 50% improvement)	1 RCT (Katz et al. 2015[7])	Oxycodone ER (40 to 160 mg/day) vs. placebo (389 patients)	Significantly more patients in the Xtampza ER group had 50% improvement in pain intensity compared with placebo group (38.3% vs 24.5%, p=0.0032).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Response (at least 30% improvement)	1 RCT (Katz et al. 2015[7])	Oxycodone ER (40 to 160 mg/day) vs. placebo (389 patients)	Significantly more patients in the Xtampza ER group had 30% improvement in pain intensity compared with placebo group (49.2% vs 33.2%; p=0.0013).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
PGIC	1 RCT (Katz et al. 2015[7])	Oxycodone ER (40 to 160 mg/day) vs. placebo (389 patients)	Significantly more Xtampza ER patients were "very much improved" (26.4% Xtampza ER, 14.3% placebo) and "improved" (40.4% Xtampza ER, 32.1% placebo) at the final visit; p<0.0001.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Quality of analgesia (overall for week 12)	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	Remoxy was rated significantly better than placebo at week 12 (LOCF) in patient assessment of quality of analgesia (p=0.004).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Global assessment of study medication (overall for week 12):	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	Remoxy was rated significantly better than placebo at week 12 (LOCF) in patient assessment of study medication(p=0.007).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Quality of life (SF-12v2, physical component subscale)	2 RCTs (Katz et al. 2015[7] and Friedmann et al. 2011[6])	Oxycodone ER vs. placebo (801 patients) Katz: 40 to 160 mg/day Friedmann: 10 to 80 mg/day	Significant between group differences were observed for the physical component score of the SF-12v2 favoring oxycodone ER Katz: 7.52±10.13 Xtampza ER, 3.62±9.43 placebo; p=0.0016 Friedmann: p=0.003	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion in one study[6]	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Quality of life (SF-12v2, mental component subscale)	2 RCTs (Katz et al. 2015[7] and Friedmann et al. 2011[6])	Oxycodone ER vs. placebo (801 patients) Katz: 40 to 160 mg/day Friedmann: 10 to 80 mg/day	One study found a significant between group difference for the mental component score of the SF-12v2 favoring oxycodone ER[7] while the other study did not[6] Katz: -2.55±10.42 Xtampza ER, 0.67±11.17 placebo; p=0.0362 Friedmann: p=0.055	Serious limitations (-1)	Serious inconsistency (-1)	No serious indirectness	Serious imprecision (-1) No measures of dispersion in one study[6]	Very low
WOMAC OA (3 subscales of pain, stiffness and physical function)	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	WOMAC subscales were numerically the same or better for Remoxy; significantly different for pain subscale only (p=0.023)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Function (RMDQ)	1 RCT (Katz et al. 2015[7])	Oxycodone ER (40 to 160 mg/day) vs. placebo (389 patients)	At week 12, there was no significant difference in change of physical disability between groups measured by RMDQ (0.4±4.83 Xtampza ER, 0.7±5.32 placebo; p=0.4555).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Gastrointestinal disorders	1 RCT (Katz et al. 2015[7])	Oxycodone ER (40 to 160 mg/day) vs. placebo (389 patients)	More Xtampza ER patients experienced GI disorders than placebo patients (24.4% Xtampza ER, 11.2% placebo)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Nausea	2 RCTs (Katz et al. 2015[7] and Friedmann et al. 2011[6])	Oxycodone ER vs. placebo (801 patients) Katz: 40 to 160 mg/day Friedmann: 10 to 80 mg/day	Both studies reported that more oxycodone ER patients experienced nausea than placebo patients. Katz: 10.9% Xtampza ER, 4.6% placebo Friedmann: 20% Remoxy, 10% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion	Low
Constipation	2 RCTs (Katz et al. 2015[7] and Friedmann et al. 2011[6])	Oxycodone ER vs. placebo (801 patients) Katz: 40 to 160 mg/day Friedmann: 10 to 80 mg/day	Both studies reported that more oxycodone ER patients experienced constipation than placebo patients. Katz: 5.2% Xtampza ER, 0.5% placebo Friedmann: 17% Remoxy, 4% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion	Low
Dry mouth	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	More Remoxy patients experienced dry mouth than placebo patients (2% Remoxy, 0% placebo)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Vomiting	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	More Remoxy patients experienced vomiting than placebo patients (14% Remoxy, 3% placebo)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Diarrhea	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	Diarrhea occurred less in Remoxy patients than placebo patients 4% Remoxy, 6% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Somnolence	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	More Remoxy patients experienced somnolence than placebo patients (11% Remoxy, 2% placebo)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Dizziness	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	More Remoxy patients experienced dizziness than placebo patients (8% Remoxy, 4% placebo)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Headache	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	No differences were reported for this outcome (5% Remoxy, 5% placebo)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low
Pruritis	1 RCT (Friedmann et al. 2011[6])	Oxycodone ER (10 to 80 mg/day) vs. placebo (412 patients)	No differences were reported for this outcome (3% Remoxy, 3% placebo)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) One single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Discontinuation	2 RCTs (Katz et al. 2015[7] and Friedmann et al. 2011[6]) (801 patients) Katz: 40 to 160 mg/day Friedmann: 10 to 80 mg/day	Oxycodone ER vs. placebo	Fewer patients in the oxycodone group discontinued compared with placebo group.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion	Low
Tapentadol Extended Release Versus Placebo								
Pain Intensity (11-point NRS)	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies and 2 RCTs (Vinik et al. 2014,[3] Schwartz et al. 2011[2]) (2,680 patients) Santos: 200–500 mg/day Vinik: 100–150 mg bid or 200–250 mg bid Schwartz: 100–250 mg bid	Tapentadol extended release (ER) vs. placebo	All three studies reported significant between group differences favoring tapentadol for higher reduction in pain intensity from baseline compared with placebo measured on an 11-point numerical rating scale. Santos: Mean difference -0.56 (95% CI: -0.92 to -0.20; I^2 =65%) Vinik: Least squares mean difference -0.95 (95% CI: -1.42 to -0.49; p<0.001) Schwartz: Least squares mean difference -1.30 (95% CI: -1.70 to -0.92; p<0.001)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Wide 95% CI in one study[1]	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Response (at least 50% pain reduction)	1 systematic review (Santos et al. 2015[1]) with an evidence base of 2 studies and 2 RCTs (Vinik et al. 2014,[3] Schwartz et al. 2011[2])	Tapentadol ER vs. placebo (2,020 patients) Santos: 200 to 500 mg/day Vinik: 100–150 mg bid or 200–250 mg bid Schwartz: 100–250 mg bid	All three studies reported tapentadol was associated with a statistically significant higher responder rate than placebo. Santos: Risk ratio (RR) 1.36 (95% CI: 1.13 to 1.64; I^2=0%; NNTB tapentadol vs. placebo for 12 weeks; 16, 95% CI: 9 to 57) Vinik: 28.9% placebo, and 40.4% tapentadol ER; p=0.015 Schwartz: 27.6% placebo, and 37.8% tapentadol ER; p=0.028	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported in 2 studies[2,3]	Low
Response (at least 30% pain reduction)	2 RCTs (Vinik et al. 2014,[3]and Schwartz et al. 2011[2])	Tapentadol ER vs. placebo (707 patients) Vinik: 100–150 mg bid or 200–250 mg bid Schwartz: 100–250 mg bid	Both studies reported tapentadol was associated with a statistically significant higher responder rate than placebo. Vinik: 45.4% placebo, 55.4% tapentadol ER; p=0.032 Schwartz: 42.2% placebo, 53.6% tapentadol ER; p=0.017	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported in 2 studies[2,3]	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
PGIC	1 systematic review (Santos et al. 2015[1]) with an evidence base of 2 studies and 2 RCTs (Vinik et al. 2014,[3] Schwartz et al. 2011[2])	Tapentadol ER vs. placebo (2,261 patients) Santos: 200–500 mg/day Vinik: 100–150 mg bid or 200–250 mg bid Schwartz: 100–250 mg bid	All three studies reported tapentadol-treated patients were more likely to consider themselves "much improved" or "very much improved" compared with placebo. Santos: RR 1.53 (95% CI: 1.28 to 1.82; I^2 =60%) Vinik: 45.3% placebo vs. 66.0% tapentadol ER; p<0.001 Schwartz: 38.4% placebo vs. 64.4% tapentadol ER; p<0.001	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported in 2 studies[2,3]	Low
Quality of life (SF-36 physical component summary score)	1 systematic review (Santos et al. 2015[1]) with an evidence base of 2 studies and 1 RCT (Vinik et al. 2014[3])	Tapentadol ER vs. placebo (1,631 patients) Santos: 200–500 mg/day Vinik: 100–150 mg bid or 200–250 mg bid	Both studies reported that tapentadol was associated with a statistically significant higher increase in SF-36 physical component summary score. Santos: MD 2.57 (95% CI: 1.69 to 3.44; I^2=0%) Vinik: Least squares mean difference 2.1 (95% CI: 0.67 to 3.57; p=0.004)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Quality of life (SF-36 role-physical and bodily pain subscales)	1 RCT (Vinik et al. 2014[3])	Tapentadol ER vs. placebo (318 patients) Vinik: 100–150 mg bid or 200–250 mg bid	Significant between group differences (favoring tapentadol) were reported for these subscales (p≤0.004).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Quality of life (EQ-5D)	1 systematic review (Santos et al. 2015[1]) with an evidence base of 2 studies and 1 RCT (Vinik et al. 2014[3])	Tapentadol ER vs. placebo (1,631 patients) Santos: 200 to 500 mg/day Vinik: 100–150 mg bid or 200–250 mg bid	One study reported significant between group differences (favoring tapentadol)[3] while one review reported no significant differences between groups.[1] Vinik: Least squares mean difference 0.10 (95% CI: 0.05 to -0.15; p<0.001)	Serious limitations (-1)	Serious inconsistency (-1)	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported in 1 study[1]	Very low
Quality of life (WOMAC)	1 systematic review (Santos et al. 2015[1]) with an evidence base of 2 studies	Tapentadol ER vs. placebo (1,313 patients) Santos: 200 to 500 mg/day	One review reported no significant differences between groups.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported	Low
Quality of life (BPI-SF)	1 RCT (Vinik et al. 2014[3])	Tapentadol ER vs. placebo (318 patients) Vinik: 100–150 mg bid or 200–250 mg bid	Significant between group differences (favoring tapentadol) for mean pain interference scores (p=0.003) and mean pain intensity subscale scores (p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Quality of life (NPSI)	1 RCT (Vinik et al. 2014[3])	Tapentadol ER vs. placebo (318 patients) Vinik: 100–150 mg bid or 200–250 mg bid	Significant between group differences (favoring tapentadol) were reported for NPSI subscales and total score (p≤0.015 for all scores).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion	Low
Incidence of TEAEs	2 RCTs (Vinik et al. 2014[3] and Schwartz et al. 2011[2])	Tapentadol ER vs. placebo (707 patients) Vinik: 100–150 mg bid or 200–250 mg bid Schwartz: 100–250 mg bid	Both studies reported rates were higher with tapentadol. Vinik: 61.2% placebo, 79.5% tapentadol Schwartz: 51.8% placebo, 70.9% tapentadol	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported in 2 studies[2,3]	Low
Treatment-emergent serious adverse events	2 RCTs (Vinik et al. 2014,[3] and Schwartz et al. 2011[2])	Tapentadol ER vs. placebo (707 patients) Vinik: 100–150 mg bid or 200–250 mg bid Schwartz: 100–250 mg bid	Rates were higher with tapentadol in both studies.	Serious limitations (-1)	No serious inconsistency	Serious indirectness	Serious imprecision (-1) No measures of dispersion reported in 2 studies[2,3]	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Discontinuation due to treatment-emergent adverse events (TEAEs)	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies and 2 RCTs (Vinik et al. 2014,[3] Schwartz et al. 2011[2])	Tapentadol ER vs. placebo (2,680 patients) Santos: 200 to 500 mg/day Vinik: 100–150 mg bid or 200–250 mg bid Schwartz: 100–250 mg bid	In one review (3 studies), tapentadol was associated with a significantly higher risk of withdrawal due to adverse events compared with placebo (RR 2.68 (95% CI: 2.05 to 3.52; I^2=0%; NNTH 10; 95% CI: 7 to 12, for 12 weeks).[1] 2 studies reported a non-significant higher risk of discontinuation due to TEAEs with tapentadol.[2,3] Vinik: 11.4% tapentadol ER, 7.9% placebo Schwartz: 11.2% tapentadol ER, 5.7% placebo	Serious limitations (-1)	Serious inconsistency (-1)	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported in 2 studies[2,3]	Very low
Serious adverse events	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	No differences were reported in incidence of serious adverse events (RR 1.01 (95% CI: 0.47 to 2.16; I^2=21%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Adverse events	1 systematic review (Santos et al. 2015[1]) with an evidence base of 2 studies	Tapentadol ER vs. placebo (1,318 patients) Santos: 200 to 500 mg/day	Significantly more participants treated with tapentadol had a higher risk of overall incidence (RR 1.25 (95% CI: 1.16 to 1.35; I^2=0%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Constipation	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	Higher risk with tapentadol (RR 2.43 (95% CI: 1.86 to 3.17; I^2=4%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Nausea	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	Higher risk with tapentadol (RR 2.81 (95% CI: 2.18 to 3.62; I^2=0%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Vomiting	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	Higher risk with tapentadol (RR 2.77 (95% CI: 1.83 to 4.21; I^2=56%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Dry mouth	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	Higher risk with tapentadol (RR 3.08 (95% CI: 1.92 to 4.94; I^2=0%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Somnolence	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	Higher risk with tapentadol (RR 3.27 (95% CI: 2.26 to 4.73; I^2=19%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Dizziness	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	Higher risk with tapentadol (RR 2.73 (95% CI: 2.08 to 3.60; I^2=13%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Fatigue	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	Higher risk with tapentadol (RR 2.15 (95% CI: 1.48 to 3.11; I^2=0%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Diarrhea	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	No differences were reported (RR 0.85 (95% CI: 0.59 to 1.23; I^2=0%),	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Headache	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	No differences were reported (RR 1.13 (95% CI: 0.91 to 1.40; I^2=44%.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Pruritus	1 systematic review (Santos et al. 2015[1]) with an evidence base of 3 studies	Tapentadol ER vs. placebo (1,974 patients) Santos: 200 to 500 mg/day	No differences were reported (RR 2.67 (95% CI: 0.85 to 8.37; I^2=72%).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Discontinuation due to adverse events	1 RCT (Schwartz et al. 2011[2])	Tapentadol ER vs. placebo (389 patients) Schwartz: 100–250 mg bid	Rates of discontinuation due to adverse events were higher with tapentadol (7.8% placebo, 14.8% tapentadol).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low
Withdrawal	1 RCT (Schwartz et al. 2011[2])	Tapentadol ER vs. placebo (389 patients) Schwartz: 100–250 mg bid	Rates for "no opioid withdrawal" were slightly higher with placebo for patients with COWS assessment who did not discontinue during the first week of the double-blind phase, and did not take opioids after discontinuation (90.5% tapentadol, 96.7% placebo).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision (-1) No measures of dispersion, one single study	Low

[a] Methodological Quality takes into account the overall risk of bias rating of all the studies included in the evidence base;

[b] Inconsistency of results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed);

[c] Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population; and

[d] Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.

AE: adverse event; API: average pain intensity; AUC: area under the curve; bid: twice a day; BPI-SF: Brief Pain Inventory-Short Form; BTDS: buprenorphine transdermal system; BTP: breakthrough pain; CGI-S: Clinical Global Impression of Illness; CI: confidence interval; COWS: Clinical Opiate Withdrawal Scale; EQ-5D: EuroQoL-5 Dimension; ER: extended release; FBT: fentanyl buccal tablets; HC-ER: hydrocodone extended release; HRQoL: health-related quality of life; LOCF: last observation carried forward; LSM: least squares mean; mg: milligram; NNTB: number needed to treat for an additional benefit; NNTH: number needed to treat for an additional harm; NRS: numerical rating scale; OA: osteoarthritis; OR: odds ratio; OROS: osmotic-controlled release oral delivery system; PAF: Patient Assessment of Function; PGA: Patient Global Assessment; PGIC: Patient Global Impression of Change; PI: pain intensity; PR: pain relief; RCT: randomized controlled trial; RMDQ: Roland Morris Disability Questionnaire; RR: risk ratio; SGAM: Subject Global Assessment of Medication; SOWS: Subjective Opiate Withdrawal Scale; SPID60: sum of the pain intensity difference 60 minutes post-dose; TEAE: treatment emergent adverse events; µg/h: micrograms per hour; WOMAC: Western Ontario McMaster Questionnaire

Table 1-b. Overall Assessment of Quality of Evidence Base (Short-term Safety)

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Buprenorphine Transdermal Delivery System Versus Placebo								
Incidence of AEs	1 RCT (Gordon et al. 2010[16])	BTDS (20, 30, or 40 µg/h) vs. placebo (78 patients)	Significantly more patients in the BTDS group reported AEs (p=0.003). 89.0% BTDS, 64.7% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Low
Nausea	1 RCT (Gordon et al. 2010[16])	BTDS (20, 30, or 40 µg/h) vs. placebo (78 patients)	Significantly more patients reported nausea in the BTDS group (p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Low
Vomiting	1 RCT (Gordon et al. 2010[16])	BTDS (20, 30, or 40 µg/h) vs. placebo (78 patients)	Significantly more patients reported vomiting in the BTDS group (p=0.008).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Low
Somnolence	1 RCT (Gordon et al. 2010[16])	BTDS (20, 30, or 40 µg/h) vs. placebo (78 patients)	Significantly more patients reported somnolence in the BTDS group (p=0.020).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Dry Mouth	1 RCT (Gordon et al. 2010[16])	BTDS (20, 30, or 40 µg/h) vs. placebo (78 patients)	Significantly more patients reported dry mouth in the BTDS group (p=0.003).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Low
Dizziness	1 RCT (Gordon et al. 2010[16])	BTDS (20, 30, or 40 µg/h) vs. placebo (78 patients)	Significantly more patients reported dizziness in the BTDS group (p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Low
Drop-out Rate Due to AEs	1 RCT (Gordon et al. 2010[16])	BTDS (20, 30, or 40 µg/h) vs. placebo (78 patients)	More patients in the BTDS group dropped out due to AEs. 21.6% BTDS, 4.4% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Low
Incidence of Serious AEs	1 RCT (Gordon et al. 2010[16])	BTDS (20, 30, or 40 µg/h) vs. placebo (78 patients)	No serious AEs were reported.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Loss to Follow-up	1 RCT (Gordon et al. 2010[16])	BTDS (20, 30, or 40 µg/h) vs. placebo (78 patients)	The same number of patients in both groups were lost to follow-up. 1.4% BTDS, 1.5% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Low
CR Oxycodone/CR Naloxone Versus Placebo								
Incidence of AEs	1 RCT (Cloutier et al. 2013[18])	CR oxycodone/ CR naloxone (20 mg/10 mg, 30 mg/15 mg, or 40 mg/20 mg every 12 h) vs. placebo (83 patients)	No significant between-group difference was reported for overall incidence of AEs (p=0.0679).	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Moderate
Somnolence	1 RCT (Cloutier et al. 2013[18])	CR oxycodone/ CR naloxone (20 mg/10 mg, 30 mg/15 mg, or 40 mg/20 mg every 12 h) vs. placebo (83 patients)	Significantly more patients in the CR oxycodone/ CR naloxone group reported somnolence (p=0.0455).	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Moderate
Drop-out Rate Due to AEs	1 RCT (Cloutier et al. 2013[18])	CR oxycodone/ CR naloxone (20 mg/10 mg, 30 mg/15 mg, or 40 mg/20 mg every 12 h) vs. placebo (83 patients)	More patients dropped out due to AEs in the CR oxycodone/ CR naloxone group. 7.2% CR oxycodone/ CR naloxone, 6.0% placebo	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Incidence of Serious AEs	1 RCT (Cloutier et al. 2013[18])	CR oxycodone/ CR naloxone (20 mg/10 mg, 30 mg/15 mg, or 40 mg/20 mg every 12 h) vs. placebo (83 patients)	The incidence of serious AEs was the same for both groups. 4.8% of patients	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Moderate
Loss to Follow-up	1 RCT (Cloutier et al. 2013[18])	CR oxycodone/ CR naloxone (20 mg/10 mg, 30 mg/15 mg, or 40 mg/20 mg every 12 h) vs. placebo (83 patients)	Fewer patients in the CR oxycodone/ CR naloxone group were lost to follow-up. 0% CR oxycodone/ CR naloxone, 2.6% placebo	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Moderate
Tramadol ER Versus Flupirtine MR								
Incidence of TEAEs	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. fllupirtine (400 mg daily) (235 patients)	Significantly more patients in the tramadol ER group experienced TEAEs (p=0.039). 34.5% tramadol, 21.0% flupirtine	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Time until TEAEs	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. fllupirtine (400 mg daily) (235 patients)	Patients in the tramadol ER group experienced TEAEs significantly sooner (p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Incidence of Serious TEAEs	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. fllupirtine (400 mg daily) (235 patients)	No serious TEAEs were reported in either group. No deaths occurred during the study.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Drop-Out Rate Due to TEAEs	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. fllupirtine (400 mg daily) (235 patients)	Significantly more patients in the tramadol ER group dropped out due to TEAEs (p=0.017). 12.1% tramadol ER, 3.4% flupirtine	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Nausea	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. fllupirtine (400 mg daily) (235 patients)	Significantly more patients in the tramadol ER group patients reported nausea (p<0.001). 19.0% tramadol ER, 1.7% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Vomiting	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. fllupirtine (400 mg daily) (235 patients)	Significantly more patients in the tramadol ER group reported vomiting (p<0.001). 11.2% tramadol ER, 0% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Dizziness	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. fllupirtine (400 mg daily) (235 patients)	More patients in the tramadol ER group reported dizziness (not significant). 12.9% tramadol ER, 6.0% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Fatigue	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. fllupirtine (400 mg daily) (235 patients)	No significant between group differences were reported for fatigue.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Tramadol Versus Placebo								
Incidence of AEs	1 RCT (Norrbrink and Lundeber 2009[17])	Tramadol (50–400 mg 3 times daily) vs. placebo (35 patients)	Significantly more patients in the tramadol group reported 1 or more AEs (p=0.02). 91% tramadol, 58% placebo	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Very low
Drop-out Rate Due to AEs	1 RCT (Norrbrink and Lundeber 2009[17])	Tramadol (50–400 mg 3 times daily) vs. placebo (35 patients)	More patients in the tramadol group dropped out due to AEs. 52.2% tramadol, 8.3% placebo	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Very low
Tiredness	1 RCT (Norrbrink and Lundeber 2009[17])	Tramadol (50–400 mg 3 times daily) vs. placebo (35 patients)	More patients in the tramadol group reported tiredness. 74% tramadol, 17% placebo	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Dry Mouth	1 RCT (Norrbrink and Lundeber 2009[17])	Tramadol (50–400 mg 3 times daily) vs. placebo (35 patients)	More patients in the tramadol group reported dry mouth. 52% tramadol, 25% placebo	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Very low
Dizziness	1 RCT (Norrbrink and Lundeber 2009[17])	Tramadol (50–400 mg 3 times daily) vs. placebo (35 patients)	More patients in the tramadol group reported dizziness. 52% tramadol, 25% placebo	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Very low
Sweating	1 RCT (Norrbrink and Lundeber 2009[17])	Tramadol (50–400 mg 3 times daily) vs. placebo (35 patients)	More patients in the tramadol group reported sweating. 39% tramadol, 25% placebo	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Very low
Constipation	1 RCT (Norrbrink and Lundeber 2009[17])	Tramadol (50–400 mg 3 times daily) vs. placebo (35 patients)	More patients in the tramadol group reported constipation. 35% tramadol, 33% placebo	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Nausea	1 RCT (Norrbrink and Lundeber 2009[17])	Tramadol (50–400 mg 3 times daily) vs. placebo (35 patients)	More patients in the tramadol group reported nausea. 39% tramadol, 25% placebo	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Very low
Tramadol ER Versus Placebo (Short-Term Safety)								
Incidence of TEAEs	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. placebo (236 patients)	Significantly more patients (p=0.001) experienced TEAEs with tramadol ER. 34.5% tramadol ER, 15.8% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Time until TEAEs	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. placebo (236 patients)	Patients in the tramadol ER group experienced TEAEs significantly sooner than patients in the placebo group (p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Incidence of Serious TEAEs	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. placebo (236 patients)	No serious TEAEs were reported in any group. No deaths occurred during the study.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Drop-Out Rate Due to TEAEs	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. placebo (236 patients)	Significantly more patients in the tramadol ER group dropped out due to TEAEs (p=0.014).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Loss to Follow-Up	Schiphorst Preuper et al 2014[13]	Tramadol ER (37.5 mg twice daily or 75 mg thrice daily) vs. placebo (50 patients)	4% of patients in the tramadol ER group were lost to follow-up due to family circumstances.	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Small single study, no measures of dispersion reported	Moderate
Incidence of AEs	Schiphorst Preuper et al 2014[13] Hyup Lee et al 2013[14]	Tramadol ER (37.5 mg twice daily or 75 mg thrice daily;[13] 75–150 mg twice daily[14]) vs. placebo (295 patients)	Both studies reported more AEs in the tramadol ER group. Schiphorst Preuper: 50% tramadol ER, 24% placebo Hyup Lee: 83.2% tramadol ER, 54.2% placebo	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for 2 studies[13,14]	Moderate
Incidence of Serious AEs	Hyup Lee et al 2013[14]	Tramadol ER (75–150 mg twice daily) vs. placebo (245 patients)	A serious AE was reported in 1 patient in the tramadol ER group, and it was considered unrelated to the study drug. No deaths occurred during the study.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Drop-Out Rate Due to AEs	Schiphorst Preuper et al 2014[13] Hyup Lee et al 2013[14]	Tramadol ER (37.5 mg twice daily or 75 mg thrice daily;[13] 75–150 mg twice daily[14]) vs. placebo (295 patients)	Both studies reported higher drop-out rates due to AEs in the tramadol ER group. Schiphorst Preuper: 8% tramadol ER, 0% placebo Hyup Lee: 19.2% tramadol ER, 5.0% placebo	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for 2 studies[13,14]	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Nausea	Hyup Lee et al 2013[14] Überall et al 2012[15]	Tramadol ER (75–150 mg twice daily;[14] 200 mg daily[15]) vs. placebo (481 patients)	Both studies reported a higher incidence of nausea in the tramadol ER group. Hyup Lee: 36.8% tramadol ER, 10.0% placebo Überall: 19.0% tramadol ER, 2.5% placebo, p=0.001	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for 2 studies[14,15]	Low
Vomiting	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. placebo (236 patients)	Significantly more patients in the tramadol ER group reported vomiting (p<0.001). 11.2% tramadol ER, 0.8% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Dizziness	Hyup Lee et al 2013[14] Überall et al 2012[15]	Tramadol ER (75–150 mg twice daily;[14] 200 mg daily[15]) vs. placebo (481 patients)	Both studies reported a higher incidence of dizziness in the tramadol ER group. Hyup Lee: 28.0% tramadol ER, 8.3% placebo Überall: 12.9% tramadol ER, 3.3% placebo, p=0.008	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) No measures of dispersion reported for 2 studies[14,15]	Low
Fatigue	Überall et al 2012[15]	Tramadol ER (200 mg daily) vs. placebo (236 patients)	No significant between group differences were reported for fatigue in all groups.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Headache	Hyup Lee et al 2013[14]	Tramadol ER (75–150 mg twice daily) vs. placebo (245 patients)	A higher incidence of headache was reported in the tramadol ER group. 8.8% tramadol ER, 5.0% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low
Dyspepsia	Hyup Lee et al 2013[14]	Tramadol ER (75–150 mg twice daily) vs. placebo (245 patients)	A similar incidence of dyspepsia was reported in the tramadol ER group. 10.4% tramadol ER, 10.0% placebo	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) Single study, no measures of dispersion reported	Low

[a] Methodological Quality takes into account the overall risk of bias rating of all the studies included in the evidence base;

[b] Inconsistency of results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed);

[c] Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population; and

[d] Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.

AE: adverse event; BTDS: buprenorphine transdermal system; CR: controlled release; ER: extended release; mg: milligram; MR: modified release; RCT: randomized controlled trial; TEAE: treatment emergent adverse event; µg/h: micrograms per hour

Appendix A. Evidence Tables

Table 2. Systematic Review/Meta-analysis (Long-term Effectiveness and Safety)

Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results
Tapentadol Versus Placebo			
Reference: Santos et al. 2015[1] **Country:** Portugal **Purpose:** To determine the efficacy, safety, and tolerability of tapentadol extended-release (ER) for moderate-to-severe pain for at least three months for any musculoskeletal cause **Quality Rating:** Fair The review authors rated 2 studies as having low risk of bias (Afilalo 2010, Buynak 2010) due to incomplete outcome data; and rated 1 study as having a high risk of bias (Afilalo 2013) due to concerns regarding the outcomes selected and lacking an allocation concealment description. The authors reported finding no evidence for publication bias.	CENTRAL (the Cochrane Central Register of Controlled Trials), MEDLINE, EMBASE, Web of Science to March 2014 plus trials registers and reference lists from retrieved studies. **Inclusion/Exclusion Criteria:** Randomized controlled trials (published and unpublished, where randomisation was explicit and appropriate) comparing tapentadol with placebo, other strong analgesic agents, both or other active controls; adults aged 18 years or older with moderate-to-severe chronic musculoskeletal pain (at least 3 months) of any cause.	**Number of Patients**: 1,973 **Diagnosis**: Knee osteoarthritis (Afilalo 2010, Afilalo 2013); low back pain (Buynak 2010) **Age**: Afilalo 2013: Not reported Afilalo 2010: Aged ≥40 years Buynak 2010: Not reported **Gender**: Afilalo 2013: Not reported Afilalo 2010: Men and women Buynak 2010: Men and non-pregnant, non-lactating women **Intervention/Comparators:** Tapentadol ER (200–500 mg/day) vs. placebo Afilalo 2013: Tapentadol ER 100–250 mg twice daily (320 patients), placebo (337 patients) Afilalo 2010: Tapentadol ER 100–250 mg twice daily (346 patients), placebo (339 patients) Buynak 2010: Tapentadol ER 100–250 mg twice daily (321 patients), placebo (326 patients) **Follow-up:** 12 weeks 2 studies; 15 weeks (Afilalo 2010)	**Pain** (3 studies, 1,973 patients): At 12 weeks, tapentadol extended release was associated with a statistically significantly higher reduction in pain intensity from baseline compared with placebo. Mean Difference (MD) on the 11-point numerical rating scale (NRS) -0.56 (95% CI: -0.92 to -0.20; I^2=65%). **Responders Rate (at least 50% pain reduction)** (2 studies, 1,313 patients): tapentadol was associated with a statistically significantly higher responder rate than placebo. Risk ratio (RR) 1.36 (95% CI: 1.13 to 1.64; I^2=0%; NNTB tapentadol vs. placebo for 12 weeks; 16, (95% CI: 9 to 57). **Patient Global Impression of Change (much or very much improved)** (2 studies, 1,554 patients): Tapentadol-treated were more likely to consider themselves much or very much improved. RR 1.53 (95% CI: 1.28 to 1.82; I^2=60%). **Quality of Life** (2 studies, 1,313 patients): Statistically significant between group differences were reported for one (SF-36) of three functional health status and well-being scores (EQ-5D, SF-36, WOMAC). Tapentadol was associated with a statistically significant higher increase in SF-36 physical component summary score. MD 2.57 (95% CI: 1.69 to 3.44; I^2=0%). No significant differences were demonstrated for WOMAC or EQ-5D. **Discontinuation Due to Treatment-emergent Adverse events** (3 studies, 1,975 patients): Tapentadol was associated with a significantly higher risk of withdrawal due to adverse events compared with placebo. RR 2.68 (95% CI: 2.05 to 3.52; I^2=0%); NNTH 10; (95% CI: 7 to 12, for 12 weeks). **Adverse events:** Tapentadol was associated with a higher risk of overall incidence of adverse events

Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results
			(2 studies, 1,318 patients). RR 1.25 (95% CI: 1.16 to 1.35; I^2=0%). No differences were reported in incidence of serious adverse events (3 studies, 1,974 patients). RR 1.01 (95% CI: 0.47 to 2.16; I^2 21%). Tapentadol was associated with a higher risk of constipation RR 2.43 (95% CI: 1.86 to 3.17; I^2=4%), nausea RR 2.81 (95% CI: 2.18 to 3.62; I^2=0%), vomiting RR 2.77 (95% CI: 1.83 to 4.21; I^2=56%), dry mouth RR 3.08 (95% CI: 1.92 to 4.94; I^2=0%), somnolence RR 3.27 (95% CI: 2.26 to 4.73; I^2=19%), dizziness RR 2.73 (95% CI: 2.08 to 3.60; I^2=13%), and fatigue RR 2.15 (95% CI: 1.48 to 3.11; I^2=0%). There were no differences for diarrhea RR 0.85 (95% CI: 0.59 to 1.23; I^2=0%), headache RR 1.13 (95% CI: 0.91 to 1.40; I^2=44%), and pruritus RR 2.67 (95% CI: 0.85 to 8.37; I^2=72%).

CI: confidence interval; EQ-5D: EuroQol-5; ER: extended release; MD: mean difference; mg: milligram; NNTB: number needed to treat for an additional benefit; NNTH: number needed to treat for an additional harm; NRS: numerical rating scale; RR: risk ratio; SF-36: 36-item short form; WOMAC: Western Ontario McMaster Questionnaire

Table 3-a. Individual Studies (Long-term Effectiveness and Safety)

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Buprenorphine Transdermal Delivery System Versus Placebo			
Reference: Breivik et al. 2010[11] **Country:** Denmark, Finland, Norway, Sweden **Study Design:** Randomized controlled trial **Purpose:** To study the efficacy and tolerability of a low dose 7-day buprenorphine transdermal delivery system (BTDS), added to a NSAID or coxib regimen, in opioid-naïve patients with moderate to severe OA pain **Quality Rating:** Fair Intent-to-treat analyses. Double blind. Computerized block randomization. Patients were required to stop taking other opioids for at least 3 weeks prior to study. Clinical, but not demographic, characteristics varied at baseline. Attrition >20% in both groups.	**Number of Patients:** 199 (100 BTDS, 99 placebo) **Diagnosis:** OA pain of the hip or knee **Age in Years (Mean±SD):** 62.96±9.9 BTDS, 62.9±9.0 placebo **Gender:** BTDS (72.00% female, 28.00% male), placebo (64.65% female, 35.35% male **Inclusion Criteria:** Men and women over the age of 40; fulfilled American College of Rheumatology Criteria for OA; experienced pain from relevant joint for at least 1 year prior to enrollment; radiographic evidence of OA of the hip and/or knee, as defined by Grades II to IV of the Kellgren and Lawrence scale, evaluating the extent of narrowing of joint space, presence of osteophytes, and possible deformity of bone ends; taking NSAIDs or coxibs for their OA pain for at least 1 month prior to screening visit at a stable frequency and dose, and at least half the maximum allowed daily dose which gives an anti-inflammatory effect; continued to experience at least moderate pain when walking on a flat surface, in spite of treatment with NSAIDs or coxibs; were willing to continue their treatment with NSAID or coxib, at a stable frequency and dose, until the end of the double-blind phase; those who had been using intermittently low-potent opioids (e.g., tramadol, low dose codeine) were willing to discontinue this regimen from the screening visit until the completion or discontinuation visit and take paracetamol tablets provided by the Sponsor as intermittent analgesic rescue; those who were receiving transcutaneous nerve stimulation or biofeedback prior to study entry were willing to discontinue this therapy for the duration of the study.	**BTDS Group**: Iinitial dose 5 µg/h; titration of BTDS permitted for entire study; up-titration could be carried out only after at least 3 days treatment at any given dose; 5, 10, or 20 µg/h maintenance doses **Placebo Group:** Titrated as study drug; identical in appearance and packaging to study drug **Supplemental Analgesia:** 0.5 g paracetamol tablets provided; taken every 4-6 h as needed, up to 4 g daily allowed; subjects had to abstain from paracetamol rescue for at least 24 h before each study visit; maintained stable dose and frequency of NSAID or coxib analgesic **Follow-up:** 6 months **Primary Efficacy Outcome:** Change in WOMAC OA index pain subscale from baseline to 6 months or withdrawal **Secondary End Points:** • Change from baseline in WOMAC OA stiffness and functional ability subscale scores • Change from baseline in WOMAC OA index total score • Pain intensity on movement on NRS-11 scale • Daily rescue medication use • Number of nights woken because of pain • Quality of sleep • PGIC in overall status at 6 months	**WOMAC OA Pain Subscale (change from baseline to 6 months or withdrawal):** Patients in the buprenorphine group "showed a clear tendency for greater reduction in pain." However, "the differences at the end of treatment did not quite reach statistical significance." -3.2 BTDS, -2.3 placebo Difference -0.86 (95% CI: -1.76 to 0.04; p=0.061) • **Subgroup analysis of patients with OA grade II and III:** Significant between-group difference favoring BTDS Difference -1.00 (95% CI: -1.94 to -0.05; p=0.039) **WOMAC OA stiffness subscale:** No significant between-group difference reported. Difference -0.18 (95% CI: -0.56 to 0.19; p=0.331) **WOMAC OA functional ability subscale:** No significant between-group difference reported. Difference -2.90 (95% CI: -5.86 to 0.06; p=0.055) **WOMAC OA overall score:** No significant between-group difference reported. Difference -3.95 (95% CI: -8.06 to 0.16; p=0.0592) **Pain intensity NRS-11 Scale:** A significant between-group difference was reported for pain intensity favoring BTDS. Difference between means -0.5 (95% CI: -0.95 to -0.05; p=0.0292) **Daily Rescue Medication Use:** No significant between-group difference.

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	Exclusion Criteria: Had been treated with strong opioid analgesics (e.g., morphine, oxycodone, methadone, fentanyl-patch); treated regularly with weak opioid analgesics such as tramadol, or codeine, for longer than 3 weeks prior to screening visit; if any intermittent, short-term, treatment with weak opioids could not be discontinued for the duration of the study; history of other chronic condition(s) for which they required frequent analgesic therapy (e.g., headaches, migraine, gout); were scheduled for any major surgery that would fall within the screening phase or the double-blind phase of the study; if transcutaneous nerve stimulation or biofeedback prior to enrollment could not be discontinued for the duration of the study; if the investigator deemed that the patient had any contraindication to treatment with opioid medication, such as history of alcohol or substance abuse; any other clinically significant disease or any reduced organ function; using antidepressants, antiepileptic drugs, steroids, hypnotics (that may increase respiratory depression of buprenorphine); if the patient, or any close relatives, had long QT-syndrome, were on anti-arrhythmic medication (Class IA or Class III), or had any unstable or symptomatic cardiac abnormality	• Time until completion or withdrawal from study	Mean 2 tablets of 0.5 g paracetamol per day for all patients **Number of Nights Woken Because of Pain:** No significant between-group difference was reported. p=0.8542 **Quality of Sleep:** No significant between-group difference was reported. **PGIC:** A significant between-group difference was reported favoring BTDS. 2.9 vs. 3.4, p=0.0171 **Time Until Completion or Withdrawal from Study:** 157 days BTDS (164 for hip, 143 for knee); 167 days placebo (almost identical for hip and knee) "None of the following variables analysed had a significant effect on the treatment duration: primary site of pain, i.e. knee or hip (p=0.3617); adverse events (p=0.2618); seasons (p=0.9872); patient gender (p=0.1207), or the WOMAC score for pain at baseline (p=0.3928)." **AEs:** More patients in the BTDS group reported AEs. 92.0% BTDS, 73.7% placebo **Application Site Reactions:** Similar rates of application site reactions occurred in both groups. 35% BTDS, 30% placebo **Constipation:** 24.0% BTDS, 5.1% placebo **Nausea:** 37.0% BTDS, 10.0% placebo **Vomiting:** 16.0% BTDS, 2.0% placebo **Dizziness:** 25.0% BTDS, 9.1% placebo **Headache:** 7.0% BTDS, 6.1% placebo **Drop-out Rate Due to AEs:** More patients in the BTDS group dropped out due to AEs. 31% BTDS, 2% placebo

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			Serious AEs: Similar incidence of serious AEs were reported with BTDS. 5% BTDS, 4% placebo **Attrition:** 54% BTDS, 34% placebo **Lost to Follow-Up:** not reported
Reference: Steiner et al. 2011[12] **Country:** USA **Study Design:** Randomized controlled trial **Purpose:** To evaluate the efficacy, tolerability, and safety of BTDS in opioid-naïve patients who had moderate to severe chronic LBP **Quality Rating:** Fair Efficacy analyses on full analysis population (patients who were randomized and received at least 1 dose of double-blind study drug). Safety analyses on safety population (all patients who received BTDS and had at least 1 safety assessment during the open-label period). Opioid washout period. Similar clinical and demographic characteristics at baseline. Attrition >20% in both groups.	**Number of Patients:** Run-in phase safety population: 1,024 Randomized phase safety population: 539 (256 BTDS, 283 placebo) Full analysis population: 541 (257 BTDS, 284 placebo) **Diagnosis:** Moderate to severe LBP for >3 months **Age in Years (Mean±SD):** Full analysis population: 48.8±12.55 BTDS, 50.0±13.37 placebo **Gender:** Full analysis population: BTDS (52% female, 48% male), placebo (58% female, 42% male) **Inclusion Criteria:** At least 18 years old; LBP must have been the predominant pain condition and must have lasted several hours daily; opioid naïve (receiving less than 5 mg of oxycodone or the equivalent in the 14 days prior to screening, did not have a history of daily opioid use of 5 mg or more of oxycodone or the equivalent for 3 months prior to screening, and who, in the opinion of the investigator, were not opioid dependent at time of entry to the study), had not benefited from, or had not tolerated nonopioid therapy; deemed by the investigator to be appropriate candidates for around-the-clock opioid analgesic regimen; patients with LBP related to nonmalignant conditions (e.g., intervertebral disc disease, spinal stenosis, spondylolysis, spondylolisthesis, OA) were eligible for inclusion **Exclusion Criteria:** Presented with radicular symptoms, acute spinal cord compression,	**BTDS Group:** 5 µg/h initial dose; 10 or 20 µg/h maintenance dose, depending on analgesic response **Placebo Group:** Placebo similar to study drug **Supplemental Analgesia:** Sponsor provided IR oxycodone 5 mg capsules to be taken as needed up to 10 mg/day for rescue medication during first 6 days of double-blind phase; acetaminophen up to 2 g/day and ibuprofen up to 800 mg/day provided for weeks 2–12 of the double-blind phase; supplemental analgesia was to be suspended for 30 hours prior to assessing pain at study visits; adjunct stable therapies for back pain (e.g., physical therapy, biofeedback therapy, acupuncture therapy, herbal remedies) were allowed if they were initiated at least 14 days before study entry; NSAIDs, aspirin, COX-2 inhibitors were permitted only for conditions other than chronic pain (e.g., headache, fever, cardiovascular disease prophylaxis); muscle relaxants were permitted for muscle spasms; stable regimens of antidepressants and anticonvulsants for uses other than pain treatment were allowed; oral corticosteroids, glucosamine, chondroitin sulfate, transcutaneous electrical nerve stimulation, biofeedback, physical therapy, and relaxation therapy were allowed, provided treatment was considered stable by the investigator	**Average Pain Over the Last 24 Hours at Week 12 (NRS-11):** Difference -0.58 (95% CI: -1.02 to -.014; p=0.0104) **MOS Sleep Scale:** Difference -4.4 (95% CI: -7.5 to -1.3; p=0.0062) **Mean Daily Number of Tablets of Supplemental Analgesia:** Difference -0.124 (95% CI: -0.296 to 0.048; p=0.1586) **TEAEs:** 55% BTDS, 52% placebo **Nausea:** 13% BTDS, 11% placebo **Dizziness:** 4% BTDS, 1% placebo **Headache:** 5% BTDS, 5% placebo **Serious AEs:** No deaths during the study. 4 patients with serious AEs in run-in phase. 5 patients with serious AEs in double-blind phase (3 BTDS, 2 placebo). **Drop-out Rate Due to AEs:** 16% BTDS, 7% placebo **Attrition:** Run-in phase: 47%; double-blind phase: 34% BTDS, 30% placebo **Lost to Follow-Up:** 1 patient in the BTDS group was lost to follow-up during the double-blind phase

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	acute compression fracture; seronegative spondyloarthropathy, acute nerve root compression, cauda equine compression, fibromyalgia, reflex sympathetic dystrophy or causalgia (complex regional pain syndrome), diabetic amyotrophy, meningitis, discitis, gout, pseudogout, psoriatic arthritis, active Lyme disease, rheumatoid arthritis or other inflammatory arthritis, trochanteric bursitis, ischial tuberosity bursitis, neuropathic conditions, or back pain caused by secondary infection, tumor, or postherpetic neuralgia; had surgery to treat back within 6 months of screening or planned to have such surgery during study period; QTc value of >480 ms and not eukalemic; required treatment with Class IA or Class III antiarrhythmic medications	**Follow-up:** 12 weeks **Primary Efficacy Outcome:** Average pain over that last 24 hours at week 12 on NRS-11 **Secondary End Points:** • Sleep disturbance subscale of MOS Sleep Scale at weeks 4, 8, 12 Mean daily number of tablets of nonopioid supplemental analgesia weeks 2 through 12	
Fentanyl Buccal Tablets Versus Placebo			
Reference: Farrar et al. 2010[10] **Country**: U.S. **Study Design:** 3 randomized, double-blind, placebo-controlled, multi-crossover clinical trials **Purpose**: To evaluate the continued efficacy, safety, and tolerability of fentanyl buccal tablets (FBT) compared with placebo in opioid-tolerant adults with non-cancer-related breakthrough pain (BTP) **Quality Rating**: Fair Intent to treat analysis; adequate randomization methods; patients served as own controls; follow-up on <80% of patients	**Number of Patients:** 79 patients (full analysis), 148 patients (safety analysis) The full analysis set (N=79) included all patients who treated ≥1 BTP episode with FBT and ≥1 BTP episode with placebo during double-blind treatment and recorded the pretreatment PI score for each of these episodes. The safety analysis set (N=148) included patients who were enrolled in the dose-titration phase and received ≥1 dose of FBT. **Source of Chronic Pain (Full Analysis):** Back pain (47%), neck pain (11%), fibromyalgia (8%), traumatic injury (8%), complex regional pain syndrome (9%), osteoarthritis (6%), diabetic peripheral neuropathy (1%), other pain (10%) **Age (Years):** 51.2±9.6 **Gender (Full Analysis):** 37% male, 63% female **Inclusion Criteria:** The study population included men and women between 18 and 80 years of age who had a ≥3-month history of chronic pain and 1–4 episodes of BTP per day.	**Fentanyl/Placebo Group**: Nine blinded tablets (six FBT and three matching placebo) to be used for the next nine sequential BTP episodes. Patients were randomly assigned in a balanced crossover scheme to one of three blinded treatment sequences to ensure that patients did not receive placebo for two consecutive BTP episodes. Each RCT assessment period continued long enough to allow patients to treat nine episodes of BTP, or for a maximum of 10 days. Of the 105 patients who found successful doses during the titration phase, most attained adequate pain relief with the 2 highest doses (800 µg [49%], 600 µg [23%]). Other doses providing adequate relief included 400 µg (14%), 200 µg (11%), and 100 µg (3%). Most patients continued the FBT dose during the 3 subsequent RCT assessment periods. Of the 81	**$SPID_{60}$:** Sum of the pain intensity difference 60 minutes post-dose was significantly greater for BTP episodes treated with FBT compared with placebo after week 12 (mean±SD 7.7±6.2 FBT, 4.6±4.7 placebo; p<0.001). Similar findings were demonstrated (after week 12) 30 minutes after drug administration (2.8±2.8 FBT, 1.6±2.0; p<0.01), 90 minutes after drug administration (12.9±9.6 FBT, 7.5±7.5 placebo; p ≤0.001), and 120 minutes after administration (18.2±13.1 FBT, 10.4±10.3 placebo; p ≤0.001). **Proportion of Episodes with a PID of ≥33% (453 FBT Episodes, 226 Placebo Episodes):** The proportion of BTP episodes with ≥33% improvement in PI was greater after FBT compared with placebo, beginning at 5 minutes post dose (7% FBT, 3% placebo; p=0.0150) and increasing to a maximum of 90 minutes (54% FBT, 31% placebo; p<0.0001).

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	Patients were permitted to have any type of chronic pain, except headache or migraine. Enrollment of patients with low back pain was limited to ≤60% of the study population. Eligible patients had to be opioid tolerant, defined as receiving ≥60 mg/day of oral morphine, ≥25 µg/hour of transdermal fentanyl, ≥30 mg/day of oxycodone, ≥8 mg/day of hydromorphone, or an equivalent, stable daily dose of another opioid for ≥30 days before enrolling in the study. The BTP that patients had to experience was defined as temporary flares of severe or excruciating pain, each lasting <4 hours, and that were at least partially relieved by their current supplemental opioid. **Exclusion Criteria:** Individuals with uncontrolled (defined as an average pain intensity (PI) score > 6/10 on the NRS during the 24 hours before enrollment), or rapidly escalating pain inconsistent with BTP; a known allergy or another contraindication to any ingredient in the study drug; history of alcohol or other substance abuse during the past 5 years; presence of cardiopulmonary disease or other medical or psychiatric disorder that, in the investigator's opinion, would have significantly increased the risks associated with opioid treatment or compromised the collection of study data. Patients were also excluded if they were expected to have surgery during the study, had participated in a previous FBT study, had taken an investigational drug in the previous 30 days, or were pregnant or lactating.	patients who completed the third RCT assessment period, 10 patients increased their dose due to lack of efficacy and 1 decreased it due to side-effects. On average, patients treated 2.4 BTP episodes per day. **Supplemental opioids (commonly taken (≥5%), *n* (%)** Oxycodone 63 (43) Hydrocodone 55 (37) Morphine 17 (11) Fentanyl 11 (7) Hydromorphone 7 (5) **Follow-up:** 12 weeks (3 double-blind periods) **Primary Efficacy Outcome**: Sum of the pain intensity differences (PID) 5 to 60 minutes post-dose ($SPID_{60}$) during the final double-blind period. Pain intensity difference (PID) was calculated for each episode as the baseline PI score minus the PI score at each time point after study drug was taken. **Secondary End Points**: Pain relief (PR), meaningful PR, proportion of episodes with a PID of ≥33% and ≥50%, and $SPID_{30}$, $SPID_{90}$, and $SPID_{120}$ calculated at 30, 90, and 120 minutes, respectively after study drug administration.	**Proportion of Episodes with a PID of ≥50% (453 FBT Episodes, 226 Placebo Episodes):** The proportion of BTP episodes with ≥50% improvement in PI reached statistical significance at 15 minutes post dose with FBT compared with placebo (17% vs 10%; p=0.0216) and was maintained at all subsequent time points. **Pain Relief (PR):** The average onset of PR began at 5 minutes (12% FBT, 7% placebo; p=0.0175), with meaningful PR by ≤10 minutes (14% FBT, 7% placebo; p=0.0006). **Supplemental Medication:** Supplemental medication was used in fewer BTP episodes treated with FBT compared with episodes treated with placebo (26% FBT, 40% placebo treated; Odds ratio (OR) 1.8640 (95% CI: 1.3 to 2.7; p=0.0007). **Discontinued Due to AEs (Overall):** 10% **Discontinued Due to Adverse Event (Dose-titration Phase):** 6% **Discontinued Due to Adverse Event (12-week Treatment Phase):** 4% **AEs occurring in ≥5% (overall):** **Nausea:** 15% **Dizziness:** 11% **Somnolence:** 8% **Vomiting:** 5% **Arthralgia:** 5% **Back pain:** 4% **Gastroenteritis viral:** 4% **Influenza:** 4% **Constipation** was only reported in 3% of patients. **Application-site AEs (Overall):** 7%; erythema (4 patients), swelling (2 patients), erythema and discoloration (1 patient),

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			erythema and vesicles (1 patient), and irritation, reaction, and ulcer (1 patient each). **TEAEs (Overall):** 45% **Serious AEs:** 7%; pneumonia (2 patients), obliterative bronchiolitis, pyelonephritis, abuse of study medication, panic attack, biliary dilatation, neuropathic pain, device-related infection, osteomyelitis, and multiple drug overdoses occurred in 1 patient each. Accidental overdose occurred in 1 patient who developed pneumonia. The authors noted that "it is not known what the relative contributions of study medication or other opioids were to these events." **Drug Abuse:** 1 patient consumed all their opioid medication (FBT, oxycodone, and Oxycocet) over a short period of time and suffered withdrawal symptoms after finishing her medications.
Hydrocodone Versus Placebo			
Reference: Hale et al. 2015[4] **Country:** U.S. **Study Design:** Randomized controlled trial **Purpose:** To evaluate the efficacy and safety of hydrocodone ER tablets compared with placebo to treat moderate-to-severe chronic pain in patients with osteoarthritis (OA) or low back pain (LBP) **Quality Rating:** Fair All randomized patients who received at least one dose of study medication during the double-blind treatment period were evaluable for primary and	**Number of Patients:** 293 patients (146 hydrocodone ER, 147 placebo) **Diagnosis:** OA or LBP **Type of Pain:** 71% LBP, 29% OA hydrocodone ER; 72% LBP, 28% OA placebo **Duration Since Diagnosis, Years (Mean±SD):** 12.1±10.0 hydrocodone ER, 12.5±9.1 placebo **Age, Years (Mean±SD):** 53.6±10.4 hydrocodone ER, 52.7±12.1 placebo) **Female Gender:** 60% hydrocodone ER, 59% placebo **Opioid Experience**: Half naïve, half experienced **Inclusion Criteria:** Individuals aged 18–80 years they had pain of ≥3 months' duration associated with osteoarthritis or LBP pain and an average pain intensity (API) score ≥5 on an	**Hydrocodone ER Group**: Hydrocodone ER tablets at doses of 15–90 mg administered every 12 hours: 27% 30 mg/day, 26% 60 mg/day, 22% 90 mg/day, 15% 120 mg/day, 11% 180 mg/day **Placebo Group**: Matching active drug every 12 hours **Supplemental Analgesia**: First 2 weeks of the double-blind period, patients were permitted hydrocodone/acetaminophen 5 mg/325 mg every 4-6 hours as needed (total daily hydrocodone dose of 30 mg). During week 3 to study end, patients were permitted to administer hydrocodone/acetaminophen tablets	**Pain (Mean Change in API):** No significant difference between hydrocodone ER and placebo (p=0.134) were demonstrated at week 12. Post hoc analysis indicated that the change in weekly API was significantly lower with hydrocodone ER when excluding the lowest dose (15 mg); LSM, -0.20 vs. 0.40; p=0.032). Significant between group differences (favoring hydrocodone ER) were reported at week 2 (LSM: -017 vs. 0.14 [p=0.049]) and week 8 (LSM: -0.61 vs. 0.02 [p=0.002]). **Response (Proportion of Patients with ≥30 Increases from Baseline in Weekly API):** Significantly more patients receiving placebo had >33% increase in weekly API

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
secondary efficacy analyses; randomization code generated by study sponsor (reviewed by independent statistician); treatment allocation via IVRS; comparable characteristics between groups entering double-blind phase; follow-up on <80% of patients.	eleven-point NRS during the previous 24 hours; women with a negative pregnancy test at screening. **Exclusion Criteria:** Individuals with a primary painful condition related to a source of chronic pain other than OA or LBP, if they had a recent history (≤5 years) or current evidence of alcohol or other substance abuse (except nicotine or caffeine), or were taking >135 mg/day of oxycodone, or equivalent, during the 14 days before screening; any medical or psychiatric disease that could compromise data collection or any cardiopulmonary disease that would significantly increase the risk of treatment with opioids; a positive urine drug screen that was not medically explainable; active malignancy, human immunodeficiency virus, or surgery planned during the study; treatment with a monoamine oxidase inhibitor within 14 days; any clinically significant deviation from normal in physical examination and/or clinical laboratory test values; and any hypersensitivities, allergies, or other contraindications to any ingredient in the study medication.	5 mg/325 mg as needed (up to a total daily hydrocodone dose of 10 mg). NSAIDs were also permitted on an as-needed basis (e.g., ibuprofen at a maximum dosage of 2,400 mg/day). **Follow-up:** 12 weeks **Primary Efficacy Outcome**: Change from baseline (final visit of the open-label titration period) to week 12 in the mean weekly average pain intensity (API). **Secondary End points**: • Change from baseline in the weekly average of daily API scores at weeks 1, 2, 4, and 8 • Percentage of patients with 33% and 50% increases from baseline in weekly API at weeks 1, 2, 4, 8, and 12 • Change from baseline in the weekly average of daily WPI scores at weeks 1, 2, 4, 8, and 12 • Use of supplemental opioid medication during the double-blind treatment period • Function measured by the Patient Assessment of Function (PAF) and Clinician Assessment of Patient Function (CAPF) questionnaires, completed at weeks 4, 8, and 12 • Clinical Global Impression of Severity of Illness (CGI-S) questionnaire at weeks 1, 2, 4, 8, and 12 • Brief Pain Inventory-Short Form (BPI-SF) at weeks 1, 2, 4, 8 and 12 • Short Form (SF-36) Health Survey at week 12	at week 2 (22% vs. 11%; p=0.016) and week 12 (24% vs. 11%; p=0.017). **Response (Proportion of Patients with ≥50% Increases from Baseline in Weekly API):** Significantly more patients receiving placebo had >50% increase in weekly API at week 8 (18% vs. 6%; p=0.005) and week 12 (15% vs. 6%; p=0.041). **WPI**: Mean weekly WPI was significantly lower with hydrocodone ER at week 2 (0.27 vs. -0.15; p=0.025), week 8 (0.00 vs. -0.68; p=0.004) and week 12 (-0.03 vs. -0.60; p=0.025). **Supplemental Analgesia**: Supplemental analgesia was higher with placebo (86% vs. 79%). From weeks 1 to week 12, mean daily dose of opioid rescue medicine (hydrocodone equivalent dose) ranged from 2.2 mg to 5.4 mg and 2.0 mg to 3.5 mg for the placebo and hydrocodone groups, respectively. **PAF:** No significant differences were reported between hydrocodone ER and placebo **CAPF:** No significant differences were reported between hydrocodone ER and placebo **CGI-S:** No significant differences were reported between hydrocodone ER and placebo **BPI-SF:** No significant differences were reported between hydrocodone ER and placebo **SF-36:** No significant differences were reported between hydrocodone ER and placebo **Serious TEAE:** acute pancreatitis (1 hydrocodone patient, 2 episodes). The

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			patient eventually developed chronic pancreatitis. **Serious AEs (open label):** 1% opioid experienced **Serious AEs (double blind):** 6 patients (3 [2%] each group) **Adverse Events**: **Any AE:** 62% placebo, 64% hydrocodone **Nausea:** 6% placebo, 13% hydrocodone **Headache:** 5% placebo, 7% hydrocodone **Back pain:** 5% placebo, <1% hydrocodone **Constipation:** 5% placebo, 13% hydrocodone **URTI:** 5% placebo, 5% hydrocodone **Vomiting:** 3% placebo, 6% hydrocodone **Dry mouth:** 1% placebo, 1% hydrocodone **Fatigue:** 1% placebo, <1% hydrocodone **Dizziness:** <1% placebo, 2% hydrocodone **Pruritus:** <1% placebo, 2% hydrocodone **Somnolence:** <1% placebo, 2% hydrocodone **Discontinued Due to AEs:** 60 patients (48 open label, 12 double-blind [9 hydrocodone ER, 3 placebo]) **Discontinued Due to AEs (Open Label):** 33 opioid naïve, 15 opioid experienced **AEs Leading to Discontinuation in at Least 2 Patients (Open Label):** Nausea (17 patients), somnolence (14 patients), vomiting (6 patients), dizziness (6 patients), constipation (5 patients), headache (3 patients), and 2 patients each due to fatigue, decreased appetite, sedation, insomnia, nervousness, and hyperhidrosis

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			AEs Leading to Discontinuation in at Least 2 Patients (Double-blind): Somnolence (2 patients) **Withdrawal:** Mean SOWS scores, mean COWS scores and proportion of patients in each category of withdrawal symptoms (normal, mild, moderate, moderately severe, or severe withdrawal) were similar between groups at each visit. Patients categorized by their physicians as having "normal opioid withdrawal symptoms" was similar between groups (95% hydrocodone ER, 97% placebo). No individual was categorized as having moderately severe/severe withdrawal symptoms at any time point. **Aberrant Drug-related Behaviors:** Start of open label: 22 patients (15 hydrocodone ER, 7 placebo) had positive results for aberrant drug-use behaviors, as indicated by SOAPP-R total score ≥18 and COMM total score ≥9. Start of double blind (week 2): SOAPP-R total scores for a majority (~75%) of patients were <18 (71% hydrocodone ER, 78% placebo), predictive of a low risk for aberrant drug-related behaviors. Endpoint: 72% of patients had no indication of aberrant drug-use behavior; 210 patients (100 hydrocodone ER, 110 placebo) had SOAPP-R total score <18 and COMM total score <9. **Inappropriate Opioid Use Behaviors:** Start of open label: 3 patients (2 hydrocodone ER, 1 placebo) had positive results for inappropriate opioid use behaviors (SOAPP-R total score ≥18 and ABC total score ≥3). Endpoint: Most patients had no indication of inappropriate opioid use; 212 patients (101

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			hydrocodone, 111 placebo) had SOAPP-R total score <18 and ABC total score <3. **Diversion:** 4 patients; 3 reported theft of rescue medication, 1 returned unknown medication instead of hydrocodone ER. **Loss of Study Drug (Hydrocodone ER, Rescue Medication/Placebo):** 35 (<9%) patients (29 hydrocodone ER, 8 placebo, 4 rescue medication).
Reference: Rauck et al. 2014[5] **Country:** U.S. **Study Design:** RCT **Purpose:** To determine the safety and efficacy of hydrocodone (HC) ER (HC-ER) in opioid-experienced adults with moderate-to-severe chronic LBP (CLBP) **Quality Rating:** Fair Intent to treat analysis; randomization or treatment allocation not described, comparable characteristics between groups during maintenance phase except for gender; follow-up on <80% of patients	**Number of Patients:** 302 patients (151 HC-ER, 151 placebo) **Diagnosis:** CLBP **Age, Years (Mean±SD):** 50.4±10.94 HC-ER, 50.8±12.37 placebo **Male Gender:** 38.4% HC-ER, 51% placebo **Opioid Experience:** 100% **Race (White):** 81.5% HC-ER, 79.5% placebo **Average PI score at Screening (before titration):** 6.9±1.5 HC-ER, 6.9±1.4 placebo **Average PI Score (after titration):** 3.1±0.9 HC-ER, 3.1±1.0 placebo **Pre-study Opioid Usage (mg/day Morphine Sulfate Equivalents):** 76.8±47.8 HC-ER, 79.2±46.5 placebo; most frequently reported prior opioid medication was HC-APAP, tramadol and oxycodone/APAP **Inclusion Criteria:** Males and nonpregnant, non-lactating females aged 18–75 years; generally healthy but opioid-experienced with a diagnosis of moderate-to-severe CLBP for at least several hours a day for ≥3 months, and had an average pain score of ≥4 on the NRS for the past 24 hours of screening, prior to baseline. **Exclusion Criteria:** Individuals with a history of opioid abuse or illicit drug or alcohol abuse in the past 5 years; a history of intolerance to HC or APAP; comorbid conditions that could interfere with CLBP pain assessment or the	**Hydrocodone Group**: HC-ER (Zohydro® ER; Zogenix, Inc., San Diego, CA) as 10-, 20-, 30-, 40-, and 50-mg capsules. Mean total daily dose (TDD) of 119 mg, doses ranging from 40 to 200 mg per day. **Placebo Group**: Blister packs containing matching placebo **Supplemental Analgesia:** Rescue medication (a maximum of two tablets of HC 5 mg/APAP 500 mg per day) was allowed for both treatment groups during the treatment period. **Mean TDD of Hydrocodone Rescue Medicine**: 6.0±3.4 mg HC-ER, 7.5±3.9 mg placebo **Rescue Medication Use:** Days 1 to 14 (blinded tapering): 1.0±0.6 HC-ER, 1.1±0.6 placebo Days 15 to 85 (drug tapering completed): 0.9±0.6 HC-ER, 1.1±0.6 placebo **Follow-up:** 85 days **Primary Efficacy Outcome**: Mean change in API from baseline to day 85 on the 11-point NRS **Secondary End Points**:	**Pain (Mean Change in API):** A significantly greater mean change in average daily PI score from baseline to day 85 was demonstrated in in the placebo group (0.48±1.563 HC-ER, 0.96±1.550; least squares mean change 0.48 HC-ER, 0.95 placebo, p=0.008). **Response (≥30 Average PI Score Improvement):** Significantly more responders were demonstrated in the HC-ER group (68% HC-ER, 31% placebo; p<0.001). **Response (≥50 Average PI Score Improvement):** Significantly more responders were demonstrated in the HC-ER group (48% HC-ER, 23% placebo; p<0.001). **SGAM (Satisfaction):** Significantly more HC-ER patients were satisfied with pain medication at day 85 compared with placebo patients (0.8±1.3 HC-ER, 0.0±1.4 placebo; p<0.001). **TEAEs (Conversion/Titration (C/T) phase, 510 Randomized and Nonrandomized Patients):** **Constipation:** 56 (11%) **Nausea:** 50 (9.8%) **Somnolence:** 24 (4.7%) **Fatigue:** 21 (4.1%)

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	ability to swallow, absorb, metabolize, or excrete HC-ER; uncontrolled blood pressure; body mass index >45 kg/m^2; clinically significant abnormality in clinical chemistry, hematology, or urinalysis; a history of major depressive disorder that was poorly controlled with medication; or a HADS score >12.	• Percent responders with a ≥30 average PI score improvement from screening to day 85 • Subject Global Assessment of Medication (SGAM) to assess subject satisfaction with pain medication measured at screening, baseline, and day 85 (higher mean score indicative of greater satisfaction with treatment)	**Headache:** 19 (3.7%) **Dizziness:** 17 (3.3%) **Dry mouth:** 16 (3.1%) **Vomiting:** 14 (2.7%) **Pruritus:** 13 (2.5%) **Insomnia:** 12 (2.4%) **Diarrhea:** 11 (2.2%) **Back pain:** 4 (0.8%) **Urinary tract infection:** 4 (0.8%) **Withdrawal syndrome:** 3 (0.6%) **Hypoacusis:** 3 (0.6%) **Sinusitis:** 2 (0.4%) **TEAEs (Treatment Phase):** Significantly more HC-ER patients experienced at least 1 TEAE (60% HC-ER, 44% placebo; p=0.006). **Constipation:** 7.9% HC-ER, 0% placebo (p<0.001) **Nausea:** 7.3% HC-ER, 3.3% placebo **Somnolence:** 0.7% HC-ER, 0% placebo **Fatigue:** 0.7% HC-ER, 1.3% placebo **Headache:** 0% HC-ER, 1.3% placebo **Dizziness:** 2.0% HC-ER, 0.7% placebo **Dry mouth:** 0 both groups **Vomiting:** 4.6% HC-ER, 0.7% placebo **Pruritus:** 0 both groups **Insomnia:** 2.0% HC-ER, 4.6% placebo **Diarrhea:** 2.6% HC-ER, 5.3% placebo **Back pain:** 4.0% HC-ER, 3.3% placebo **UTI:** 5.3% HC-ER, 2.0% placebo **Withdrawal Syndrome:** 0.7% HC-ER, 6.0% placebo (p=0.019) **Hypoacusis:** 3.3% HC-ER, 2.6% placebo

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			Sinusitis: 2.0% HC-ER, 2.6% placebo **Discontinuation Due to TEAEs:** 9% during the C/T phase, 4% during the treatment phase **TEAEs Leading to Discontinuation (C/T Phase):** Nausea (3%), constipation (1%) and vomiting (1%) **TEAEs Leading to Discontinuation (Treatment Phase):** 1 HC-ER patient each due to back pain and diarrhea, 4 placebo patients due to withdrawal syndrome, 5 additional placebo patients discontinue due to TEAEs (not specified) **Discontinuation:** 17.9% HC-ER, 60.9% placebo **Discontinuation Due to Serious AEs (C/T Phase):** 1 patient due to anxiety possibly related to HC-ER **Discontinuation Due to AEs (Maintenance):** 1.3% HC-ER, 3.3% placebo **Discontinuation Due to Efficacy:** 9.3% HC-ER, 42.4% placebo **Discontinuation Due to Opioid Withdrawal:** 0 HC-ER, 4.6% placebo **Discontinuation Due to Depression:** 0% HC-ER, 0.7% placebo **Lost to Follow-up:** 0.7% HC-ER, 0 placebo

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OROS Hydromorphone Versus Placebo			
Reference: Vojtassak et al 2011[8] **Country:** Czech Republic, Romania, Slovakia, UK **Study Design:** RCT **Purpose:** To compare the analgesic effect of flexibly titrated OROS hydromorphone hydrochloride and placebo for moderate-to-severe pain induced by osteoarthritis (OA) of the hip or knee that has not been adequately controlled with NSAIDs or paracetamol **Quality Rating:** Fair Intent-to-treat analysis. Double blind. Computer-generated randomization schedule prepared by an independent statistician; block randomization, stratified by OA of the hip or knee; study sites received blocks of study medication. Clinical and demographic characteristics were similar at baseline. Opioid washout period. Attrition >20% in both groups (39.6% OROS hydromorphone, 22.1% placebo)	**Number of Patients:** 288 (139 OROS hydromorphone, 149 placebo) **Diagnosis:** Moderate-to-severe pain (mean weekly score of ≥5 on Brief Pain Inventory [BPI] scale) induced by OA of the hip (26%) or knee (74%) for >3 months **Age in Years (Median [Range]):** 65.0 (43–85) OROS hydromorphone, 66.0 (40–87) placebo **Gender:** OROS hydromorphone (77% female, 23% male), placebo (68% female, 32% male) **Inclusion Criteria:** Pain from OA of the hip or knee for >3 months; pain must not have been adequately controlled with daily analgesic (NSAID or paracetamol) for the month before beginning the study **Exclusion Criteria:** Regular treatment with an opioid in the 4 weeks before the screening visit (infrequent use of tramadol, codeine, tilidine, dihydrocodeine for no more than 10 days in the 4 weeks before the screening visits was acceptable); any other continuous pain that stood out in comparison to OA pain (e.g., fibromyalgia, cervical radiculopathy, chronic LBP); any of the following for 6 months before entering study: major trauma to target joints, infection in target joints, hyaluronan injections in target joints, arthrodesis in the year or arthroscopy in the 2 months before entering the study, planned treatment that could have altered the degree of pain within the study period, treatment with buprenorphine, nalbuphine, pentazocine; corticosteroid injections in the 3 months before the start of the study	**OROS Hydromorphone Group:** 4 mg qd; if pain control was unsatisfactory, dose titrated 3–4 days after randomization until week 4 of the study with interval so at least 3–4 days between dose increments; possible doses were 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, 32 mg (maximum); patients without sufficient analgesia at 32 mg were withdrawn and tapered off **Placebo Group:** Placebo matched for color and size **Supplemental Analgesia:** Discontinued weak opioids at the screening visit (week 1); subjects taking NSAIDs or paracetamol remained on stable doses; paracetamol (4 g per day until day 8 and 2 g per day for remainder of study) allowed as rescue medication **Follow-up:** 16 weeks **Primary Efficacy Outcome:** Mean change from baseline to week 16 in "pain on average" on the BPI scale; pain assessed using all BPI items at weeks 0, 4, 8, 12, and 16 **Secondary End Points:** • Dropout rate due to AEs • Change from baseline in functionality using the total score of the Western Ontario and McMaster Universities (WOMAC) OA index • Changes from baseline of the pain subscales of the WOMAC OA index and the HRQoL instrument short form (SF)-36 and pain-related items measured on the BPI scale overall safety and tolerability of the drug	**Pain (Mean Change±SD] in Pain on Average in BPI at 16 Weeks):** No significant between-group difference was reported at 16 weeks (-2.4±2.1 OROS hydromorphone, -2.6±2.3 placebo; difference -0.2365 (95% CI: -0.5357 to 0.0627; p=0.1212). • **BPI subscales (Mean±SD):** No significant between-group differences were reported for BPI subscales pain at its worst in the last 24 hours (-2.4±2.5 OROS hydromorphone, -2.7±2.6 placebo), pain at its least in the last 24 hours (-1.7±2.2 OROS hydromorphone, -1.6±2.6 placebo), or pain right now (-2.6±2.6 OROS hydromorphone, -2.4±2.7 placebo). **Dropout Rate Due to AEs:** More patients in the OROS hydromorphone group (25.9%) dropped out due to AE than the placebo group (4.7%). **WOMAC OA Index (Mean Change±SD):** No significant between-group difference was reported in functionality by WOMAC OA total scores (-5.36±5.99 OROS hydromorphone, -5.16±6.15 placebo). • **Pain Subscale:** No significant between-group difference was reported by pain subscale scores of WOMAC OA (-3.74±4.49 OROS hydromorphone, -3.86±4.52 placebo). **SF-36 Pain Subscale (Mean Change±SD):** No significant between-group difference was reported in the SF-36 pain subscale (17.50±20.48 OROS hydromorphone, 19.47±23.50 placebo). **HRQoL (Mean Change±SD):** No significant between-group differences were reported in the physical functioning subscale

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			(13.59±19.71 OROS hydromorphone, 14.72±24.08 placebo) or in the social functioning subscale (7.29±23.42 OROS hydromorphone, 9.55±24.11 placebo). **TEAEs:** More patients reported TEAEs in the OROS hydromorphone group (35% mild, 33% moderate, 14% severe) than the placebo group (30% mild, 12% moderate, 4% severe). Possible, probable, or very likely drug-related TEAEs were reported more often by patients in the OROS hydromorphone group (78%) than the placebo group (37%). Drug-related TEAEs were most frequently reported as related to the gastrointestinal or nervous systems. **Serious TEAEs:** Serious TEAEs were reported in 2.9% of patients (10 events) in the OROS hydromorphone group and 4.7% of patients (9 events) in the placebo group. One death occurred in the placebo group, which was "not considered related to study." **Attrition:** 39.6% OROS hydromorphone, 22.1% placebo **Concomitant Analgesic Medication Use:** NSAID: 84.78% OROS hydromorphone, 79.87% placebo Paracetamol: 17.39% OROS hydromorphone, 16.78% placebo Any analgesic: 96.38% OROS hydromorphone, 92.62% placebo
Reference: Hale et al 2010[9] **Country:** USA **Study Design:** RCT **Purpose:** To evaluate the efficacy and safety of once-daily OROS hydromorphone	**Number of Patients:** 266 (133 OROS hydromorphone ER, 133 placebo); 268 patients were randomized (134 in each group) but 1 did not receive any study medication (HC) and 1 had missing baseline NRS scores (PBO) so excluded from ITT; 447 patients included in the titration/conversion phase	**OROS Hydromorphone ER Group:** Titrated/converted to daily dose of OROS hydromorphone that was about 75% of the equianalgesic dose of their previous total daily opioid use. Patients who were taking ≥12 mg and ≤64 mg of OROS hydromorphone per day were	**Pain (Mean Change in Weekly Patient Diary NRS Scores from Baseline to Week 12 or Final Visit):** A significant between-group difference was reported favoring OROS hydromorphone over placebo ($p<0.001$) for mean change in pain intensity. The median change from baseline

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extended release (ER) in the treatment of opioid-tolerant patients with chronic moderate-to-severe LBP **Quality Rating:** Fair Intent-to-treat analysis. A randomization number was assigned on day 1 of the double-blind phase via an interactive voice response system to encode the patient's assignment to one of the two treatment groups, according to the computer-generated randomization schedule. Double blind until database lock. Baseline clinical and demographic characteristics similar between two groups. Analgesic washout period. Attrition above 50% in double-blind phase for both groups.	**Diagnosis:** Chronic LBP for >6 months **Age in Years (Mean±SD):** 47.8±10.5 OROS hydromorphone ER, 49.4±10.6 placebo **Gender:** OROS hydromorphone (45.9% female, 54.1% male), placebo (54.9% female, 45.1% male) **Inclusion Criteria:** Male and female patients, aged 18–75 years with a documented diagnosis of moderate-to-severe chronic LBP for at least 3 hours per day, 20 days per month, for 6 months; pain classified as non-neuropathic (classes 1 and 2) or neuropathic (classes 3, 4, 5, and 6) based on the Quebec Task Force Classification of Spinal Disorders; on daily opioid treatment with ≥60 mg oral morphine equivalent (≥12 mg hydromorphone), but ≤320 mg morphine (≤64 mg hydromorphone) per day within 2 months prior to screening visits; on stable doses of all prior analgesics for at least 2 weeks prior to screening visit; negative serum pregnancy test at the screening visit for women of childbearing potential (including those who had a tubal ligation surgery); women agreed to use a medically acceptable method of contraception (birth control pills or patches, vaginal rings, diaphragm with vaginal spermicide, intrauterine devices, progestin implant or injection) throughout the entire study period Double-blind phase: patients were taking ≥12 mg and ≤64 mg of hydromorphone ER per day; patients remained on the same dose without change for at least 7 consecutive days (stable dose period); patients took a mean of ≤2 tablets of rescue medication hydromorphone immediate release (IR) per day during the stable dose period; patients had adequate pain control as indicated by a mean pain intensity score ≤4 on the pain intensity NRS during the stable dose period; patients answered 'yes' to the question 'Has this medication helped your	eligible to enter double-blind phase. Patients maintained stable doses over double-blind phase **Placebo Group:** Over-encapsulated placebo matching drug. Patients were tapered off OROS hydromorphone ER over 14 weeks without breaking the double blind until they received just placebo. **Supplemental Analgesia:** Hydromorphone immediate release (2, 4, or 8 mg) was allowed as rescue medication during all phases of the study. Patients were permitted a mean of 6 or fewer rescue tablets per day during week 1, mean of 4 or fewer per day during week 2, and a mean of 2 or fewer per day for the rest of the study. **Follow-up:** 12 weeks **Primary Efficacy Outcome:** Mean change from baseline to week 12 or final visit of the double-blind phase in weekly pain intensity NRS scores recorded by patients daily in a paper diary **Secondary End Points:** • Mean change from baseline to week 12 of the double-blind phase in weighted mean pain intensity NRS score based on pain intensity NRS scores recorded in patient diaries • Mean change from baseline to each visit in pain intensity during double-blind phase based on the pain intensity NRS scores recorded in the office • Time to treatment failure as determined by study discontinuation due to lack analgesic efficacy, AEs, or use of rescue medication	was 0.2 units for the OROS hydromorphone group and 1.6 units for the placebo group. **Weighted Mean Pain Intensity (Mean Change from Baseline to Week 12 Using Patient Diary NRS Scores):** A significant between-group difference was reported favoring OROS hydromorphone over placebo (p<0.001) for change in pain intensity. A significantly larger increase (p<0.001) in the placebo group (1.2) over the OROS hydromorphone group (0.4) was reported for change in mean weighted pain intensity. **Pain Intensity (Mean Change from Baseline to Each Visit in Weekly NRS Scores Recorded in the Office):** Significant between-group differences were reported favoring OROS hydromorphone over placebo (p<0.05) for change in pain intensity from baseline to each weekly visit for every week except week 3. **Time to Treatment Failure:** A significant between-group difference was reported for time to discontinuation due to treatment failure, with failure occurring sooner and more frequently in the placebo group than the OROS hydromorphone group (p<0.001). **PGA (Mean Changes from Baseline):** A significant between-group difference was reported favoring OROS hydromorphone over placebo (p<0.001) in PGA scores from baseline to week 12. **RMDQ (Mean Changes from Baseline):** Significant between-group differences were reported favoring OROS hydromorphone over placebo (p<0.05) for mean weekly changes from baseline in RMDQ scores for weeks 1, 2, 3, 8, and 12 (or final visit). No significant between-group differences were reported for mean weekly changes

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	pain enough so that you would continue to take the medication?'; patients had no side-effects that were intolerable or that could impact their ability to complete the study **Exclusion Criteria:** Any other chronic pain condition that would have interfered with the assessment of LBP; undergone a surgical procedure for back pain within 6 months prior to screening visit; active diagnosis of fibromyalgia, complex regional pain syndrome (including reflex sympathetic dystrophy or causalgia), acute spinal cord compression, severe or progressive lower extremity weakness or numbness, bowel or bladder dysfunction as a result of cauda equina compression, diabetic amyotrophy, meningitis, diskitis, back pain stemming from a secondary infection or tumor, or pain caused by a confirmed or suspected neoplasm; impaired gastrointestinal function; major psychiatric condition; clinically significant anxiety or depression; clinically significant abnormal laboratory results; received monoamine oxidase inhibitors within 14 days prior to screening visit or had no bowel movement within 3 days, or bowel obstruction within 60 days, prior to screening visit	• Mean changes from baseline in PGA (patient's overall impression of the study drug) • Rescue medication use, which included the proportion of patients requiring any rescue medication, the cumulative total number of rescue medication tablets taken, and the mean number of rescue medication tablets used per day • Mean changes from baseline in RMDQ total scores Proportion of total study dropouts in each treatment group	from baseline in RMDQ scores for weeks 4, 6, or 10. A significant between-group difference was reported favoring OROS hydromorphone over placebo ($p<0.005$) for median change of RMDQ scores from baseline to week 12 (or final visit). **Rescue Medication Use:** • **Proportion of Patients Requiring Any Rescue Medication:** No significant between-group difference was reported for proportion of patients requiring any rescue medication (OROS hydromorphone 96.2%, placebo 97.0%). • **Total Number of Rescue Medication Tablets Taken:** The total number of rescue medication tablets taken was not reported for either group. • **Mean Number of Rescue Medication Tablets Used Daily:** No significant between-group difference was reported for mean number of rescue medication tablets used daily (OROS hydromorphone 0.8 n=66, placebo 1.2 (n=44); p=0.49). According to the protocol, patients were limited to 2 tablets of rescue medication per day after week 2 of the study. **AEs:** • **Conversion/titration phase:** 55.3% of patients experienced at least one AE • **Double-blind phase (134 patients per group):** In the OROS hydromorphone group, 47.8% of patients experienced at least 1 AE; in the placebo group, 54.5% of patients did. 26.9% of patients in the OROS hydromorphone group and 32.1% of patients in the placebo group

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			experienced AEs that were considered related to study medication. **TEAEs:** • **Conversion/titration phase (447 patients):** 43.0% of patients experienced at least 1 TEAE and 11.4% discontinued due to TEAEs. The most commonly reported TEAEs occurring in more than 5% of patients were constipation (15.4%), nausea (11.9%), somnolence (8.7%), headache (7.8%), and vomiting (6.5%). • **Double-blind Phase:** The most commonly reported TEAEs occurring in more than 5% of patients of either group were drug withdrawal syndrome, nausea, constipation, vomiting, arthralgia, headache, insomnia, diarrhea, and back pain. "Adverse events that occurred at notably higher rates in the hydromorphone ER group compared with the placebo group included: constipation (7.5 vs. 3.7%), sinusitis (4.5 vs. 0.7%), and arthralgia (6.0 vs. 2.2%)." **Serious AEs:** • **Conversion/titration Phase:** 1.1% of patients had a serious AE. No deaths were reported. • **Double-blind Phase:** Six patients in the OROS hydromorphone group experienced serious AEs including vomiting and diarrhea, acute abdominal pain, cellulitis of the ear, headache, and worsening of preexisting bipolar disorder (worsening hallucinations and suicidal ideation). Four patients in the placebo group experienced serious AEs including diarrhea and dehydration, nephrolithiasis, deep vein thrombosis,

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			and possible drug withdrawal syndrome (emesis, renal failure, hypotension, and dehydration). No deaths were reported. **AEs Leading to Discontinuation:** • **Conversion/titration Phase:** 13.0% of patients discontinued due to AEs. • **Double-blind Phase:** AEs led to discontinuation for 5.2% of patients in the OROS hydromorphone group and 2.2% of patients in the placebo group. **TEAEs for OROS Hydromorphone:** • **Double-blind phase:** The most commonly reported TEAEs occurring in more than 5% of patients were drug withdrawal syndrome (9.7%), nausea (9.0%), constipation (7.5%), vomiting (6.0%), arthralgia (6.0%), headache (5.2%), and insomnia (5.2%). **Attrition:** 50.4% OROS hydromorphone ER, 66.9% placebo. A significant between-group difference was reported in attrition rates favoring placebo (p<0.01). The most common reason for discontinuation in both groups was lack of analgesic efficacy (11.9% OROS hydromorphone ER, 29.9% placebo). **Lost to Follow-Up:** 2.2% OROS hydromorphone, 1.5% placebo
Oxycodone Extended Release Versus Placebo			
Reference: Katz et al. 2015[7] **Country:** U.S. **Study Design:** RCT **Purpose:** To evaluate the analgesic efficacy of Xtampza ER compared with placebo in opioid-experienced and opioid-naive patients with moderate-to severe CLBP, requiring	**Number of Patients:** 389 (193 Xtampza ER, 196 placebo) **Diagnosis:** Moderate-to-severe CLBP **Age, Years (Mean±SD):** 49.2±13.3 Xtampza ER, 49.9±12.6 placebo) **Male Gender:** 46.6% Xtampza ER, 47.4% placebo **Opioid Naive:** 49.7% Xtampza ER, 49% placebo)	**Xtampza ER Group**: Abuse-deterrent formulation of extended-release oxycodone (Xtampza ER) – 20mg, 30 mg, 40 mg, 60 mg, 80 mg taken every 12 hours (TDD: 40 mg, 60 mg, 80 mg, 120 mg, or 160 mg) **Placebo Group**: Matching active drug containing identical microspheres with the exception of oxycodone taken every 12 hours	**Pain (API):** At week 12, the estimated pain score (ITT) was significantly higher for placebo patients (mean±SE 1.85 ±0.22 placebo, 0.29±0.15 Xtampza ER; mean difference -1.56±0.27 (95% CI: -2.1 to -1.1; p<0.0001). This positive effect of Xtampza ER remained in all sensitivity analyses (including nonmixture mixed model

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
continuous ATC opioid analgesia for an extended period of time. **Quality Rating:** Fair Intent to treat analysis; adequate randomization methods (block randomization scheme in a 1:1 ratio; stratification by prior opioid experience; treatment allocation via interactive web response system; comparable characteristics between groups entering double-blind phase; follow-up on <80% of patients	**Quality of Life Baseline (SF-12x2), PCS (Mean±SD):** 33.7±10.2 Xtampza ER, 34.4±10.3 placebo **Quality of Life Baseline (SF-12x2), MCS (mean±SD):** 55.0±10.0 Xtampza ER, 55.6±9.7 placebo **RMDQ Baseline (Mean±SD):** 8.4±5.0 Xtampza ER, 8.4±5.4 placebo **Inclusion Criteria:** Males and nonpregnant females aged 18 to 75 years at the time of consent with a clinical diagnosis of moderate-to-severe CLBP (i.e., pain intensity score of ≥5 to ≤9 on an 11-point pain intensity-NRS [PI-NRS]) for a minimum of 6 months before the screening visit. Both opioid-experienced and opioid-naive patients were enrolled; opioid-experienced patients were defined as patients on a daily dose of opioid medication ≥30 and ≤240 mg/d of morphine sulfate equivalents for a minimum of 14 days before the screening visit; patients who were on an opioid regimen for <14 days were excluded from participation. Opioid-naive patients were on 0 to 10 mg/d morphine sulfate equivalent for 14 days or more before the screening visit. Opioid-naive patients must have had moderate-to severe pain warranting ATC opioid medication, as determined by well-experienced investigators, for an extended period of time (i.e., for at least the duration of the study), and have failed previous therapy with APAP or NSAIDs (i.e., had moderate-to-severe pain while on APAP and/or NSAIDs), or were unable to tolerate NSAIDs. Key inclusion criteria were classification of back pain by the investigator as nonmalignant and nonneuropathic (classes 1 or 2), neuropathic (class 3), or symptomatic for more than 6 months after low back surgery (class 9) based on the Quebec Task Force classification. Any adjunct therapy for back pain such as physical therapy, biofeedback therapy, transcutaneous	**Supplemental Analgesia**: APAP was available as rescue medication **Follow-up:** 12 week double-blind, 14 week follow-up phone call **Primary Efficacy Outcome**: change in API (change in PI-NRS scores from randomization baseline to week 12 of the double-blind maintenance phase) **Secondary End Points**: • Quality of life measured by SF-12 question health survey, version 2 (SF-12v2); • Level of physical disability (Roland Morris Disability Questionnaire [RMDQ]); week 12 change from baseline; • Global impression of change (PGIC); • Total amount of rescue medication used; • Time-to-exit from study for all causes rom randomization baseline to week 12 of double-blind maintenance phase; • Responder analyses (cumulative distribution of patients with an improvement in pain intensity from screening baseline to week 12 of the double-blind maintenance phase and the proportion of responders with at least a 30% and at least a 50% reduction in pain intensity at week 12); • Weekly changes in pain intensity from randomization baseline to weeks 2, 4, 8, and 10	repeated measures, and LOCF/BOCF analysis of covariance). **Response (At Least 50% Improvement):** Significantly more patients in the Xtampza ER group had 50% improvement in pain intensity compared with placebo group (38.3% vs 24.5%, p= 0.0032). **Response (At Least 30% Improvement):** Significantly more patients in the Xtampza ER group had 30% improvement in pain intensity compared with placebo group (49.2% vs 33.2%; p=0.0013). **PGIC:** Significantly more Xtampza ER patients were "very much improved" (26.4% Xtampza ER, 14.3% placebo) and "improved" (40.4% Xtampza ER, 32.1% placebo) at the final visit; p<0.0001. **Discontinuation:** Fewer patients in the Xtampza ER group (36.8%) discontinued the study because of all causes compared with the placebo group (49.0%); **Time-to-exit (25% Quartile):** Longer for patients in the Xtampza ER group than placebo group (58 vs 35 days; p=0.0102). **Use of Rescue Medicine:** Mean milligrams per day was higher in the placebo group compared with Xtampza ER (189.3±317.61 placebo, 144.6±289.47 Xtampza ER; no p values were calculated). **Quality of Life (SF-12v2, PCS):** Significant between group differences were observed for the physical component score of the SF-12v2 favoring Xtampza ER (7.52±10.13 Xtampza ER, 3.62±9.43 placebo; p=0.0016). **Quality of Life (SF-12v2, MCS):** Quality of life (SF-12v2, PCS: Significant between group differences were observed for the mental component score of the SF-12v2 favoring Xtampza ER (-2.55±10.42

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	electrical nerve stimulation, acupuncture, nutraceuticals, herbal remedies, and water aerobics must have been unchanged for at least 4 weeks before the screening visit as assessed by patient interview during the screening phase and remained unchanged through the end-of-study or early discontinuation visit per protocol. **Exclusion Criteria:** Patients known to be refractory or intolerant to the analgesic effects of opioids or who had failed previous opioid therapy or had a known contraindication to any opioid or APAP, including allergy or hypersensitivity. Patients with any chronic pain condition other than CLBP who, in the investigator's opinion, would have interfered with the assessment of CLBP (e.g., osteoarthritis, rheumatoid arthritis, postherpetic neuralgia, pain associated with diabetic neuropathy, fibromyalgia, and migraine headaches requiring opioid therapy) were ineligible to participate. Additionally, any patient with a known history of alcohol or drug abuse, major depressive disorder that was not controlled with medication, or other conditions that produced significant cognitive or emotional disability were excluded.		Xtampza ER, 0.67±11.17 placebo; p=0.0362). **Function (RMDQ):** At week 12, there was no significant difference in change of physical disability between groups measured by RMDQ (0.4±4.83 Xtampza ER, 0.7±5.32 placebo; p=0.4555). **Compliance:** 99.8% both groups **AEs (Number of Events)**: 1,681 (1,197 open-label titration phase, 484 double-blind maintenance phase [293 Xtampza ER, 191 placebo]) **AEs (Percent of Patients)**: 62.4% open-label, 56.6% double-blind phase **Serious AEs:** 1.1% open-label, 1.0% double-blind **TEAEs:** 62.4% titration, 56.6% maintenance (64.8% Xtampza ER, 48.5% placebo) **TEAEs (Most Frequent):** Gastrointestinal disorders (33.5%) and nervous system disorders (29.2%) were the most frequently reported TEAEs during the open-label phase. During the double-blind maintenance phase, GI disorders were the most frequently reported TEAEs. **GI Disorders:** More Xtampza ER patients experienced GI disorders than placebo patients (24.4% Xtampza ER, 11.2% placebo) **Nausea:** More Xtampza ER patients experienced nausea than placebo patients (10.9% Xtampza ER, 4.6% placebo) **Constipation:** More Xtampza ER patients experienced constipation than placebo patients (5.2% Xtampza ER, 0.5% placebo) **Treatment-related TEAEs:** 49.5% titration, 26.7% maintenance (33.7% Xtampza ER, 19.9% placebo)

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			Serious/Severe TEAEs: 2 patients open-label (1 patient experienced gastroesophageal reflux, 1 patient experienced worsening erectile dysfunction), 1 placebo patient suffered from anxiety **TEAEs Leading to Discontinuation:** 14.2% open-label, 6.4% double-blind (7.8% Xtampza ER, 5.1% placebo) **TEAEs Leading to Death:** 1 open-label
Reference: Friedmann et al. 2011[6] **Country:** U.S. **Study Design:** RCT **Purpose:** To assess the analgesic efficacy and safety of Remoxy vs. placebo in patients with moderate-to-severe chronic pain due to OA of the hip and/or knee **Quality Rating:** Fair Intent to treat analysis; randomization and allocation methods not described; comparable characteristics between groups entering double-blind phase; 64% completed (similar between groups)	**Number of Patients:** 412 (205 Remoxy, 207 placebo) **Diagnosis:** OA knee (78% Remoxy, 79% placebo), OA hip (22% Remoxy, 21% placebo) **Age, Years (Mean±SD):** 58±7.86 Remoxy, 58.5±8.44 placebo **Male Gender:** 28% Remoxy, 32% placebo **Pre-randomization PI Score (Mean±SD):** 5.2±2.19 Remoxy, 5.4±2.11 placebo **Pre-randomization Score WOMAC Osteoarthritis Index Total Score (Mean±SD):** 1,170.2±566.69 Remoxy, 1,194.8±553.78 placebo **Inclusion Criteria:** Male or nonpregnant, non-breastfeeding females aged 40 to 75 years who had experienced moderate-to-severe chronic pain for ≥3 months owing to OA of the hip and/or knee as demonstrated by clinical and radiographic evidence according to the American College of Rheumatology criteria for diagnosis and who were regularly (≥4 days/week every week for 4 weeks prior to the screening visit) taking one or more of the following oral medication: nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, tramadol, and opioids **Exclusion Criteria:** Individuals who had a daily opioid dose equivalent of oxycodone >80 mg for ≥4 days/week during the week before the initial	**Remoxy ER Oxycodone Group:** 20 mg bid at beginning of the double-blind, titrating up/down to analgesic effect for 4 weeks (maximum, 40 mg bid; minimum, 5 mg bid); fixed dose for 8 weeks **Placebo Group:** Treated identically to patients allocated to Remoxy and permitted to request dose changes for analgesic effect for 4 weeks even though their dose was fixed. **Supplemental Analgesia:** Aspirin for cardiovascular events **Follow-up:** 12 weeks **Primary Efficacy Outcome:** Area under the curve for the change in PI score from pre-randomization to double-blind week 12 **Secondary End Points:** • Quality of analgesia; • Global assessment of study medication; • Quality of life using SF-12 Health Survey, WOMAC OA index	**Pain (Change in PI score):** Mean area under the curve (AUC) for the change in PI scores was significantly greater for Remoxy (-54.9 Remoxy, -30.4 placebo; p=0.007)) This significant difference was demonstrated at week 4 (-0.8±1.78 Remoxy, -0.0±2.09; p<0.001), week 8 (-0.8±2.01 Remoxy, -0.3±2.34 placebo; p=0.002), and week 12 (-0.7±2.05 Remoxy, -0.3±2.48; p=0.024). **Quality of Analgesia (Overall for Week 12):** Remoxy was rated significantly better than placebo at week 12 (LOCF) in patient assessment of quality of analgesia (p=0.004). **Global Assessment of Study Medication (Overall for Week 12):** Remoxy was rated significantly better than placebo at week 12 (LOCF) in patient assessment of study medication(p=0.007). **Quality of Life (SF-12, PCS Subscale):** Significantly better for Remoxy (p=0.003). **Quality of Life (SF-12, MCS Subscale):** No significant difference (p=0.055). **WOMAC OA (3 Subscales of Pain, Stiffness and Physical Function):** Numerically the same or better for Remoxy;

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	screening visit; those who had an intra-articular injection of hyaluronic acid in the hip or knee in the 6 months prior to the screening visit, or corticosteroid therapy (oral, intra-articular, or parenteral) or an epidural or intrathecal infusion of any analgesic medications in the 1 month prior to the screening visit; and those with a positive urine drug screen for opiates, amphetamines, methamphetamines, cocaine, cannabinoids, phenylcyclohexylpiperidine, or methadone at the baseline visit were excluded. A stable dose for more than 4 weeks was required for monoamine oxidase inhibitors, tricyclic antidepressants, serotonin reuptake inhibitors, or other antidepressants, gabapentin, Pregabalin, and glucosamine/chondroitin. High doses of sedatives, hypnotics, or tranquilizers as well as phenothiazines or other agents comprising vasomotor tone were excluded.		significantly different for pain subscale only (p=0.023). **Mean Daily Dose of Study Medication:** 27.5 mg bid for Remoxy, 32.8 mg bid for placebo **Discontinuation Due to AEs (Open Label):** 124 out of 146 withdrawals were due to AEs **Discontinued (Double-blind):** 34% Remoxy, 36% placebo **Discontinued Due to AEs (Double-blind):** 21% Remoxy, 11% placebo **Serious AEs:** 11 patients (4 open label, 7 double-blind [2 placebo, 5 Remoxy]) **Serious TEAEs:** 2 (1 orthostatic hypotension during open label, 1 fecaloma during double-blind) **Adverse Events (Open Label):** **Constipation:** 25% **Nausea:** 20% **Dry mouth:** 5% **Vomiting:** 5% **Diarrhea:** 1% **Somnolence:** 19% **Dizziness:** 12% **Headache:** 7% **Pruritis:** 12% **Adverse Events (Double-blind):** **Constipation:** 17% Remoxy, 4% placebo **Nausea:** 20% Remoxy, 10% placebo **Dry mouth:** 2% Remoxy, 0% placebo **Vomiting:** 14% Remoxy, 3% placebo **Diarrhea:** 4% Remoxy, 6% placebo **Somnolence:** 11% Remoxy, 2% placebo **Dizziness:** 8% Remoxy, 4% placebo **Headache:** 5% Remoxy, 5% placebo **Pruritis:** 3% Remoxy, 3% placebo

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Tapentadol Extended Release Versus Placebo			
Reference: Vinik et al. 2014[3] **Country:** U.S. **Study Design:** Randomized-withdrawal, placebo-controlled trial **Purpose:** To evaluate the efficacy and tolerability of tapentadol extended release (ER) to manage chronic pain associated with diabetic peripheral neuropathy (DPN) **Quality Rating:** Fair Intent to treat analysis; used randomly permuted blocks stratified by study site and patient's tapentadol ER dose category (100–150 mg bid or 200–250 mg bid); patient's allocated to treatment based on a computer-generated schedule using an interactive voice response system (IVRS); groups comparable at baseline for double-blind safety population; only 70% completed	**Number of Patients:** 318 (166 tapentadol ER, 152 placebo) **Diagnosis:** Type 1 or 2 diabetes and chronic painful DPN for ≥6 months **Age, Years (Mean±SD):** 58.5±10.63 tapentadol, 59.0±9.00 placebo **Gender:** Tapentadol (59.6% male, 40.4% female), placebo (57.9% male, 42.1% female) **Inclusion Criteria:** Adults ≥18 years of age with type 1 or 2 diabetes; chronic painful DPN for ≥6 months; and pain at screening; optimized diabetic regimen for ≥3 months prior to screening consisting of diet, oral hypoglycemic, or insulin therapy; ≥3-month history of analgesic use for painful DPN and dissatisfaction with current analgesic treatment (if patients were taking an opioid, a dose equivalent of oral morphine ≤160 mg/day was required); and a mean pain intensity score of ≥5 on a Likert-type 11-point numerical rating scale (NRS; 0="no pain" and 10="pain as bad as you can imagine") calculated from twice-daily pain assessments during a 3-day pain intensity pretreatment evaluation period after a 5-day washout of previous analgesic medications. **Exclusion Criteria:** History of the following: alcohol and/or drug abuse; a condition other than painful DPN that could confound the assessment/self-evaluation of pain (e.g., fibromyalgia or inflammation [e.g., rheumatoid arthritis or ankylosing spondylitis]); a significant disorder (e.g., pulmonary, gastrointestinal, endocrine, or psychiatric) that could affect study assessments or compromise safety; moderate to severe hepatic impairment or severely impaired renal function; seizure disorder or epilepsy; traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within the	**Tapentadol ER Group:** Fixed optimal dose of 100-150 mg bid or 200-250 mg bid **Placebo Group:** Down-titrated in a blinded fashion to tapentadol ER 100 mg bid for 3 days (to reduce withdrawal) then placebo (identical in appearance and packaging to tapentadol). **Supplemental Analgesia:** Tapentadol ER 25 mg bid was permitted as additional analgesia by all participants during the first 4 days and once per day from day 5 onward during the double-blind phase of the study. **Follow-up:** 12 weeks **Primary Efficacy Outcome:** Mean change in average pain intensity from baseline (start of double-blind phase) to week 12. Average pain intensity over the last 12 hours was recorded twice daily on an 11-point numerical rating scale (NRS). **Secondary End Points:** • Proportions of patients with ≥30 and ≥50% improvement in pain intensity from pretitration to week 12 of the double-blind maintenance phase; • Patient global impression of change (PGIC) at the double-blind end point; • Changes from the start of double-blind treatment to the double-blind end point in Brief Pain Inventory-Short Form (BPI-SF) pain interference and pain intensity subscale scores, subscales of the NPSI, Short Form-36 (SF-36) Health Survey subscales and summary	**Pain (Mean Change [SD] in Average Pain Intensity [LOCF] at 12 Weeks):** Significant between-group differences were reported at 12 weeks favoring tapentadol (1.30 (2.43) placebo, 0.28 (2.04) tapentadol ER; least squares mean difference, -0.95 (95% CI: -1.42 to -0.49; p<0.001). This positive effect of tapentadol remained in all sensitivity analyses (including BOCF, PMI, and WOCF). **Pain (Proportion of Patients with ≥30 Improvement in Pain Intensity):** Significant between group differences were reported favoring tapentadol (45.4% placebo, 55.4% tapentadol ER [p=0.032]). **Pain (Proportion of Patients with ≥50% Improvement in Pain Intensity):** Significant between group differences were reported favoring tapentadol (28.9% placebo, and 40.4% tapentadol ER [p=0.015]). **PGIC**: Significant between group differences were reported favoring tapentadol (percent patients reporting their PGIC status as "very much improved" or "much improved" was 45.3% placebo vs. 66.0% tapentadol ER [p<0.001]). **BPI-SF:** Significant between group differences were reported favoring tapentadol for mean pain interference scores (p=0.003) and mean pain intensity subscale scores (p<0.001). **NPSI Subscales and Total Score:** Significant between group differences were reported favoring tapentadol. (p≤0.015 for all scores).

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	past year; malignancy within the past 2 years (other than successfully treated basal cell carcinoma); extensive diabetic foot ulcers; limb amputation; or Charcot neuroarthropathy.	scale, and the EuroQol 5-Dimension (EQ-5D) health status index.	**Short Form-36 (SF-36) Health Survey Subscales and Summary Scale:** Significant between group differences were reported favoring tapentadol for physical component summary score (least squares mean difference 2.1 [95% CI: 0.67 to 3.57; p=0.004] and subscales for role-physical and bodily pain (p≤0.004 for all scores). No significant between group differences were reported for the mental component summary score and for the following subscales: physical functioning, general health, vitality, social functioning, role-emotional, and mental health. **EQ-5D Health Status Index:** Significant between-group differences were reported at 12 weeks favoring tapentadol (mean [SD] change: -0.10 [0.26] placebo, 0.00 [0.20] tapentadol ER; least squares mean difference, for tapentadol ER minus placebo, 0.10 (95% CI: 0.05 to -0.15; p<0.001). **Treatment-emergent Adverse Events (TEAE):** More than 10% of tapentadol ER patients reported nausea (21.1%) and vomiting (12.7%) during the double-blind maintenance phase. In the double-blind safety population, 61.2% placebo group and 79.5% tapentadol ER group reported one or more TEAEs. **Serious TEAEs (Open Label): I**ncluding chest pain (3 patients) and dehydration (2 patients) were reported by 2.4% of patients. **Serious TEAEs (Maintenance):** Reported by 5.9% placebo, 4.8% tapentadol ER. Coronary artery disease was the only serious TEAE reported in either group (2 patients receiving placebo). One patient taking tapentadol ER 150 mg bid died of myocardial ischemia during the open-label

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			titration period. The death was assessed as "doubtfully related to study drug; suspected cause of death, atherosclerotic coronary artery disease." **TEAEs Leading to Discontinuation**: 7.9% placebo, 11.4% tapentadol ER. Nausea was the only TEAE reported as leading to discontinuation for ≥2% of patients in either group. **TEAEs for Tapentadol ER**: The following TEAEs were reported in more than 5% of patients during the maintenance period: nausea (21.1%), vomiting (12.7%), diarrhea (6.6%), fatigue (7.2%), nasopharyngitis (5.4%), dizziness (7.2%), somnolence (6.0%), insomnia (5.4%).
Reference: Schwartz et al. 2011[2] **Country:** U.S. **Study Design:** Randomized-withdrawal, placebo-controlled trial **Purpose:** To evaluate the safety and efficacy of tapentadol ER vs. placebo in patients with moderate-to-severe chronic pain for relieving pain from DPN. **Quality Rating:** Fair Intent to treat analysis; adequate randomization methods (permuted blocks and stratification by prior opioid experience, country and dose category); treatment allocation via IVRS; comparable characteristics between groups entering double-blind phase; follow-up on <80% of patients	**Number of Patients:** 389 (196 tapentadol ER, 193 placebo) **Diagnosis:** Type 1 or 2 diabetes and painful DPN for ≥6 months **Age, Years (Mean±SD):** 59.9±10.68 tapentadol ER, 60.6±10.56 placebo **Gender:** Tapentadol ER (60.7% male, 39.3% female), placebo (60.1% male, 39.9% female) **Duration of DPN, Weeks (Mean±SD):** 284.90±258.85 tapentadol ER, 317.96±261.61 placebo **Inclusion Criteria:** Adults 18 years or older with type 1 or 2 diabetes mellitus and painful DPN for at least 6 months; HbA_{1c} no more than 11% (indicating adequate blood glucose control) for at least 3 months; at least a 3-month history of analgesic use for DPN and dissatisfaction with current treatment (if opioid, dose equivalent to ≤160 mg/day oral morphine); average pain intensity score at the start of open-label treatment of at least 5 on an 11-point NRS calculated from twice-daily pain assessments during a 3-day pain intensity pre-treatment evaluation period; postmenopausal or non-	**Tapentadol ER Group**: Fixed optimal dose of 100-250 mg bid **Placebo Group**: Blinded tapentadol ER 100 mg bid was given for 3 days before switching to placebo bid to alleviate possible withdrawal related to discontinuation. **Supplemental Analgesia**: Both groups were permitted supplemental tapentadol ER 25 mg bid during the first 4 days of double-blind treatment; thereafter, a single dose of tapentadol ER 25 mg per day was allowed as supplemental analgesia. **Follow-up:** 12 weeks **Primary Efficacy Outcome**: 11-point NRS; primary endpoint was the change from baseline in average pain intensity over the last week (week 12) of the double-blind maintenance period **Secondary End Points**: • Responder rates based on the percentage of improvement in pain	**Pain (Mean Change in Average Pain Intensity [LOCF]):** Significant between-group differences were reported at 12 weeks favoring tapentadol (least-squares mean (LSM) change 1.4 placebo, 0.0 tapentadol ER; least squares mean difference -1.30 (95% CI: -1.70 to -0.92; p<0.001). This positive effect of tapentadol remained in all imputation methods. **Pain (Proportion of Patients with ≥30 Improvement in Pain Intensity):** Significant between group differences were reported favoring tapentadol (42.2% placebo, 53.6% tapentadol ER [p=0.017]). **Pain (Proportion of Patients with ≥50% Improvement in Pain Intensity):** Significant between group differences were reported favoring tapentadol (27.6% placebo, and 37.8% tapentadol ER [p=0.028]). A statistically significant difference was reported in the distribution of responder rates for patients with any degree of

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	pregnant women practicing an effective method of birth control. **Exclusion Criteria:** Individuals who had participated in another trial within 30 days of enrollment, if they had participated in another tapentadol trial, or if they had a history of the following: alcohol and/or drug abuse, a condition other than DPN that could confound their self-evaluation of pain (e.g., fibromyalgia, rheumatoid arthritis), a significant disorder (e.g., pulmonary, endocrine, psychiatric) that could affect study assessments or compromise safety, moderate-to-severe hepatic impairment or severely impaired renal function, seizure disorder, epilepsy, traumatic brain injury, stroke, transient ischemic attack, brain neoplasm, malignancy within the past 2 years (other than successfully treated basal cell carcinoma), extensive diabetic ulcers, amputation, or Charcot joints.	intensity from pre-titration to week 12 of the maintenance period • PGIC at weeks 2, 6, and 12 (or end of treatment) of the double-blind period	improvement (pre-titration to week 12) between tapentadol ER and placebo groups (p=0.032). **PGIC:** Significant between group differences were reported at the end of the double-blind treatment favoring tapentadol (percent patients reporting their overall status as "very much improved" or "much improved" was 38.4% placebo vs. 64.4% tapentadol ER [p<0.001]). **TEAE:** Overall incidence of TEAEs was 70.9% with tapentadol ER and 51.8% with placebo. **Serious TEAEs (Open Label):** 1.4%; chest pain was reported by 2 patients, severe upper abdominal pain reported in 1 patient and considered possibly related to study drug **Serious TEAEs (Double-blind):** 1.6% placebo, 5.1% tapentadol ER **TEAEs Leading to Discontinuation (Open Label):** 20.1% patients **TEAEs Leading to Discontinuation (Double-blind):** 11.2% placebo and 5.7% tapentadol ER The following TEAEs occurred during the maintenance phase: **Any AE:** 5.7% placebo, 11.2% tapentadol **Nausea:** 1% placebo, 2% tapentadol **Vomiting:** 0 placebo, 2% tapentadol **Dizziness:** 0 placebo, 2% tapentadol **Opioid Withdrawal:** 13 patients withdrew during the first week of the double-blind period and had a follow-up COWS assessment. Of the 11 patients who did not take opioids following discontinuation, 9 patients (2 of 3 tapentadol, 7 of 8 placebo) had no opioid withdrawal.

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			For patients with COWS assessments who did not discontinue during the first week of the double-blind phase, and did not take opioids after discontinuation, 90.5% tapentadol ER and 96.7% placebo had no opioid withdrawal. The authors described all incidences of withdrawal following discontinuation of treatment with tapentadol ER as mild. **Discontinued (Double-blind):** 59 (30.1%) tapentadol ER, 59 (30.6%) placebo **AEs Leading to Discontinuation:** 15 (7.8%) placebo, 29 (14.8%) tapentadol ER **Lack of Efficacy Leading to Discontinuation:** 27 (14%) placebo, 8 (4.1%) tapentadol ER

ABC: addiction behaviors checklist; AE: adverse event; APAP: acetaminophen N-acetyl-para-aminophenol; API: average pain intensity; ATC: around the clock; BID: twice a day; BOCF: baseline observation carried forward; BPI-SF: Brief Pain Inventory-Short Form; BTDS: buprenorphine transdermal system; BTP: breakthrough pain; CAPF: clinician assessment of patient function; CGI-S: clinical global impression of illness; CI: confidence interval; CLBP: chronic low back pain; COMM: current opioid misuse measure; COWS: clinical opiate withdrawal scale; C/t: conversion/titration; DPN: diabetic peripheral neuropathy; EQ-5D: EuroQoL-5 Dimension; ER: extended release; FBT: fentanyl buccal tablets; h: hour; HADS: hospital anxiety and depression scale; HC-ER: hydrocodone extended release; HRQoL: health-related quality of life; IR: immediate release; ITT: intention to treat; IVRS: interactive voice response system; LBP: low back pain; LOCF: last observation carried forward; LSM: least squares mean; MCS: mental component summary; MD: mean difference; mg: milligram; MOS: medical outcomes study; NPSI: neuropathic pain symptom inventory; NRS: numeral rating scale; NSAIDS: nonsteroidal anti-inflammatory drugs; OA: osteoarthritis; OROS: osmotic-controlled release oral delivery system; PAF: patient assessment of function; PBO: placebo; PGA: patient global assessment; PGIC: patient global impression of change; PI: pain intensity; PID: pain intensity difference; PMI: placebo mean imputation; PR: pain relief; RCT: randomized controlled trial; RMDQ: Roland Morris Disability Questionnaire; SD: standard deviation; SF-36: short form health survey; SGAM: subject global assessment of medication; SOAPP-R: screener and opioid assessment for patients with pain-revised; SOWS: subjective opiate withdrawal scale; $SPID_{60}$: Sum of the pain intensity difference 60 minutes post-dose; TEAE: treatment emergent adverse events; URTI: upper respiratory tract infection; WOCF: worst observation carried forward; WOMAC: Western Ontario McMaster Questionnaire; WPI: worst pain intensity; µg/h: microgram/hour

Table 3-b. Individual Studies (Short-term Safety)

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Short-term Safety (Less Than 12 Weeks Follow-up)			
Reference: Gordon et al. 2010[16] **Country:** Canada **Study Design:** Randomized controlled trial **Purpose:** To assess the efficacy and safety profile of a 7-day buprenorphine transdermal system (BTDS) in adult patients with moderate-to-severe chronic LBP previously treated with 1 tablet or more daily of an opioid analgesic **Quality Rating:** Fair Intent-to-treat used for safety analysis (per protocol population used for efficacy analysis but those endpoints were not considered here due to short follow-up period). Double blind until the study completed. Computer-generated code for block randomization. Opioid washout period. No mention of potential differences between baseline clinical or demographic characteristics of treatment groups. Attrition 36.7%.	**Number of Patients:** 78 (phase 1: 39 BTDS, 39 placebo; phase 2: 35 BTDS, 29 placebo; open-label phase: 40 BTDS) **Diagnosis:** Chronic LBP of at least moderate intensity for >3 months **Age in Years (Mean±SD):** 50.7±11.9 **Gender:** 60.3% female, 39.7% male **Inclusion Criteria:** Men and nonpregnant women ≥18 years who had experienced LBP of at least moderate intensity (≥2 on a 5-point ordinal scale) for >3 months and required ≥1 tablet daily of an opioid analgesic **Exclusion Criteria:** Pain refractory to opioids; allergy to opioids or acetaminophen; patients undergoing any procedure or treatment likely to change their pain; clinically significant alternative source of pain; requiring external application of heat; suspected dependence on narcotics or alcohol; history of major psychiatric disorders; elevated liver enzymes; decreased serum potassium or magnesium; severe organ dysfunction; head injury or seizures; chronic obstructive pulmonary disease; asthma; respiratory depression; pulmonary heart disease; congestive heart failure; atrial fibrillation; myocardial ischemia; tachycardia; bradycardia; peptic ulcer disease; inflammation of the gastrointestinal tract Amended protocol 7–8 months after recruitment of first patient. Any patients with the following criteria were excluded and any already in the trial were withdrawn: personal or family history of congenital long QT syndrome*; receiving treatment with class IA or III antiarrhythmics or drugs known to prolong QT interval or induce torsades de pointes; mean QTc interval >450	**Crossover Trial:** Patients were treated in the same manner in both phases of the study; crossover occurred after 4 weeks **BTDS Group:** 10 µg/h patch for 6–8 days; titrated weekly to 20 µg/h and a maximum of 40 µg/h using 10- and 20-µg/h patches; 30 µg/h dose permitted on investigator's judgement of pain control and adverse events **Placebo Group:** Titration with corresponding placebo patches **Supplemental Analgesia:** 325–750 mg acetaminophen every 4–6 h as needed for unmanageable pain; patients were permitted to continue nonopioid analgesics at doses that were stable 2 weeks before enrollment and antidepressants or anticonvulsants at doses that were stable 8 weeks before enrollment. **Follow-up:** 8-week double-blind study phase **Open-label Extension Phase:** Patients who completed both phases of crossover were eligible to continue receiving BTDS for 6 months.	**AEs:** A significant between group difference was reported favoring BTDS over placebo (89.0% BTDS, 64.7% placebo, p=0.003) for number of patients with AEs. The most common AEs, reported by more than 5% of patients in any single group, were nausea, dizziness, skin reactions at patch site, pruritus, vomiting, somnolence, rash, dry mouth, constipation, sweating, asthenia, and headache. Significantly more BTDS patients than placebo patients suffered from nausea (p<0.001), dizziness (p<0.001), vomiting (p=0.008), somnolence (p=0.020), and dry mouth (p=0.003). No significant between group differences were reported for the other common AEs. • **Open-label Extension (OLE) Phase:** The most frequently reported AEs were nausea (37.5%), pruritus (30.0%), rash (30.0%), somnolence (20.0%), constipation (12.5%), asthenia (12.5%), headache (10.0%), and dizziness (10.0%). **Serious AEs:** No serious AEs were reported in the double-blind phase of study. • **OLE Phase:** Four patients experienced serious AEs (myocardial infarction, pneumonia, meningioma) during or shortly after the OLE phase. All were determined to be unrelated or likely unrelated to the study drug. **AEs Leading to Discontinuation:** Sixteen patients (21.6%) in the BTDS group and 3 patients (4.4%) in the placebo group withdrew from the study due to AE. The

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	ms or a single QTc interval >500 ms at any time during the crossover trial		potential significance of a between group difference was not reported. • **OLE Phase:** Seven patients (17.5%) in the OLE taking BTDS withdrew from the study due to AE that included nausea, dizziness, somnolence, asthenia, vomiting, sweating, constipation, and rash. **AEs for BTDS:** The following AEs were reported in more than 5% of patients during the study period: nausea (53.4%), dizziness (32.9%), pruritus (23.3%), vomiting (21.9%), somnolence (21.9%), rash (17.8%), dry mouth (17.8%), constipation (16.4%), sweating (13.7%), asthenia (12.3%), headache (12.3%). **Attrition:** • Phase 1: BTDS group (25.6%); 9 withdrew due to AE, 1 lost to follow-up. Placebo group (10.3%); 1 withdrew due to AE, 1 due to lack of efficacy, 1 lost to follow-up, 1 due to protocol violation • Phase 2: BTDS group (25.7%); 7 withdrew due to AE, 1 due to lack of efficacy, 1 for other reason. Placebo group (20.7%); 2 withdrew due to AE, 3 due to lack of efficacy, 1 consent withdrawn OLE phase: 32.5% withdrew; 7 due to AE, 2 lost to follow-up, 1 due to insufficient therapeutic effect, 1 due to withdrawal of consent, 1 due to withdrawal by the investigator, 1 due to remission of original indication for treatment
Reference: Cloutier et al. 2013[18] **Country:** Canada	**Number of Patients:** 83 (Phase 1: 39 CR oxycodone/CR naloxone, 44 placebo;	**Crossover Trial:** Patients were treated in the same manner in both phases of the study; crossover occurred after 4 weeks	**AEs:** No significant between-group difference was reported for overall incidence of AEs (p=0.0679).

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Study Design: Randomized controlled trial **Purpose:** To compare the analgesic efficacy and safety of CR oxycodone/CR naloxone versus placebo in patients with chronic LBP **Quality Rating:** Good Intent-to-treat analysis for safety (per protocol population used for efficacy analysis but those outcomes were not included here due to short follow-up period). Double-blind. Computer-generated randomization. Analgesic and stimulant laxative washout period. No mention of potential differences between baseline clinical or demographic characteristics of treatment groups. Attrition <20% for both groups.	phase 2: 35 CR oxycodone/CR naloxone, 33 placebo) **Diagnosis:** At least moderate chronic LBP **Age in Years (Mean±SD):** 51.3±12.5 **Gender:** 53% female, 47% male **Inclusion Criteria:** Adult (>18 years) men and non-pregnant, non-nursing women; LBP of moderate or greater intensity for previous 3 months or longer; currently taking opioids or those who had not previously responded to nonopioid therapy and now required opioids to control their pain **Exclusion Criteria:** Recently undergone or were to commence any treatments that may have involved the use of preoperative or postoperative analgesics or anesthetics or that were likely to change their pain during the study period, such as physiotherapy, corticosteroid injections or surgical procedures; required more than 12 tablets of 300 mg/30 mg acetaminophen plus codeine; had pain that was expected to be refractory to continuous opioid therapy; had a true allergy or dose-limiting intolerance to acetaminophen, oxycodone, naloxone or any other opioid; had a significant source of pain unrelated to their low back pain that could obscure the assessment of efficacy; had liver enzyme levels (alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase) higher than 2 times the upper limit of normal or compromised kidney function (serum creatinine level >20 µmol/L); had a corrected QT interval >450 ms at baseline; had known severe organ dysfunction or other conditions that, in the opinion of the investigator, adversely affected patient safety or obscured the assessment of efficacy; or had chronic obstructive pulmonary disease, severe asthma, cor pulmonale or heart failure; were receiving pharmacotherapy that may act as a central nervous system depressant; had any other	**CR Oxycodone/CR Naloxone group:** 10 mg/5 mg CR oxycodone/CR naloxone every 12 h for initial dose. Titrated weekly according to pain control and side effects to 20 mg/10 mg, 30 mg/15 mg, or a maximum of 40 mg/20 mg every 12 h. **Placebo Group:** Titrated as with study drug **Supplemental Analgesia:** Patients on stable doses of nonopioid analgesics for 2 weeks or antidepressants or anticonvulsants for 8 weeks, could continue doses as long as they were unchanged. Patients were provided with 300 mg/30 mg acetaminophen/codeine tablets for unrelieved pain (1–2 tablets every 4 h as needed). Patients were provided with 8.6 mg senna/docusate sodium tablets for constipation as required. **Follow-up:** 8 weeks **Open-label Extension Phase:** Patients who completed both phases of crossover were eligible to continue receiving CR oxycodone/CR naloxone for 6 months	The most common AEs, occurring in more than 5% of patients in either group, were nausea, constipation, diarrhea, fatigue, somnolence, vomiting, dry mouth, and abdominal pain. Significantly more patients in the CR oxycodone/CR naloxone group than the placebo group experienced somnolence (p=0.0455). No significant between-group differences were reported for any other common AEs. **AEs Leading to Discontinuation:** 7.2% of patients in the CR oxycodone/CR naloxone group and 6.0% of patients in the placebo group discontinued the study due to AEs. • **OLE Phase:** 6% of patients withdrew from the OLE phase due to AEs. **Serious AEs:** 4.8% of patients reported serious AEs (2 each in CR oxycodone/CR naloxone and placebo groups). All serious AEs were judged "not related to study medication." **AEs for CR Oxycodone/CR Naloxone:** The following AEs were reported in more than 5% of patients: nausea (12.2%), constipation (8.1%), diarrhea (5.4%), fatigue (5.4%), somnolence (5.4%), and vomiting (5.4%). **Attrition:** 10.8% of patients in the CR oxycodone/CR naloxone group and 13.3% of patients in the placebo group discontinued the study. **OLE Phase:** 20% of patients withdrew from the OLE phase.

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	disease or condition that may increase the risk of central nervous system and/or respiratory depression; active peptic ulcer disease; active inflammatory disease of the gastrointestinal tract; any disease or condition which may affect the absorption of a CR opioid; known or suspected to have psychological dependence on narcotic analgesics, other psychoactive drugs, or excessive consumption of alcohol; major psychiatric disorder such as major depression or psychotic disease; idiopathic or psychogenic pain in which nonorganic factors were considered to be predominant; currently involved in any litigation that was related to their pain, injury and/or disability		
Reference: Hyup Lee et al 2013[14] **Country:** Korea **Study Design:** Randomized controlled trial **Purpose:** To evaluate the efficacy and safety of tramadol extended release (ER) for treatment of chronic low back pain (LBP) **Quality Rating:** Fair Intent-to-treat analysis used for safety analysis; (full analysis set [pts who received study drug and had at least 1 measurement of change in average pain intensity from baseline] and per protocol patients used for efficacy analysis but those endpoints were not considered here due to short follow-up period). Double-blind until study completed and database closed. Computer-generated,	**Number of Patients:** 245 (125 tramadol, 120 placebo) **Diagnosis:** Moderate-to-severe chronic LBP **Age in Years (Mean±SD):** 59.9±10.7 tramadol ER, 60.4±9.9 placebo **Gender:** Tramadol (75.2% female, 24.8% male), placebo (74.2% female, 25.8% male) **Inclusion Criteria:** Able to walk; moderate-to-severe chronic LBP (average pain intensity ≥4.0 cm on a 10-cm VAS) despite use of NSAIDs or COX-2–selective inhibitors; pain severe enough to require continual use of analgesics for at least 3 months before screening; and a stable dose of NSAIDs or COX-2–selective inhibitors from 7 days before study drug administration and during study period **Exclusion Criteria:** Failure or discontinuation of tramadol or tramadol/acetaminophen treatment in past due to AE; use of tramadol, tramadol/acetaminophen, or opioid analgesics within 30 days, acetaminophen within 7 days, or antidepressants, anticonvulsants, or cyclobenzaprine within 3 weeks of study drug administration; tumor or infection on the meninges or spinal cord; more severe pain in	**Tramadol/Acetaminophen Group:** 75 mg/650 mg qd for 3 days, 75 mg/650 mg bid for 4 days, 75–150/650–1300 mg bid depending on their level of pain control for 22 days **Placebo Group:** Placebo (identical in appearance to tramadol) **Supplemental Analgesia:** NSAIDs or COX-2–selective inhibitors maintained at stable dose; other pain relievers, physical therapy, acupuncture, Oriental medicines not permitted during test period **Follow-up:** 29 days	**AEs:** "Adverse events occurred significantly more frequently [no p-value given]" in the tramadol group (83.2%) than the placebo group (54.2%). **AEs Leading to Discontinuation:** Occurred in 19.2% of patients in the tramadol group and 5.0% of patients in the placebo group. **AEs for Tramadol ER:** The following TEAEs were reported in more than 5% of patients during the study: nausea (36.8%), dizziness (28.0%), constipation (18.4%), vomiting (16.8%), pruritus (15.2%), somnolence (14.4%), dyspepsia (10.4%), headache (8.8%). **Serious AEs:** Were reported in one patient in the tramadol ER group during the study phase. The patient received a diagnosis of breast cancer that was considered unrelated to tramadol ER. Three serious AEs occurred during the screening period, which were considered unrelated to the study. No deaths occurred during the study. **Attrition:** 26.4% of patients in the tramadol ER group and 13.3% of patients in the

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
stratified randomization plan (each center considered a stratum); block randomization code created by sponsor before study start. Clinical and demographic characteristics between groups were not significantly different at baseline. Overall attrition 20% but 26.4% in tramadol ER group.	area other than low back; neurologic deficit on the legs due to a spine lesion; pain from fibromyalgia, complex regional pain syndrome, acute spinal cord compression, cauda equina syndrome, proximal diabetic neuropathy, infection, or a tumor; underwent back surgery within past 3 months; or received a steroid injection within 4 weeks of screening		placebo group discontinued the study after randomization and the first dose.
Reference: Norrbrink and Lundeberg 2009[17] **Country:** Sweden **Study Design:** Randomized controlled trial **Purpose:** To assess the efficacy and safety of tramadol for relieving neuropathic pain after spinal cord injury (SCI) **Quality Rating:** Poor Intent-to-treat analysis. Double-blind until treatment completion. Unspecified randomization. No washout period of previous opioids. Baseline clinical and demographic characteristics similar between groups except for proportion of patients with paraplegia (48% tramadol, 67% placebo) and tetraplegia (52% tramadol, 33% placebo). Attrition higher in tramadol group (48%) than placebo group (17%).	**Number of Patients:** 35 (23 tramadol, 12 placebo) **Diagnosis:** Traumatic or non-traumatic SCI and neuropathic pain at or below level of injury **Age in Years (Mean±SD):** 51.4±11.6 tramadol, 51.2±9.7 placebo **Gender:** Tramadol (17.4% female, 82.6% male), placebo (25% female, 75% male) **Inclusion Criteria:** Signed, informed consent; SCI for more than 12 months; pain classified as neuropathic at or below level of lesion and for longer than 6 months; no known cognitive impairment; pain intensity ratings of general or worst in the last week required to be equivalent to 3 or more on Borg's Category Ratio (CR-10) scale; naïve to tramadol; no signs of intolerance to opioids in the past **Exclusion Criteria:** Pregnancy; lactation	**Tramadol Group:** 50 mg tid; increase dose by 50 mg every 5 days until maximum of 400 mg daily; patients were instructed to stop increasing dose if optimal pain relief obtained or AE became intolerable **Placebo Group:** Placebo identical in appearance **Supplemental Analgesia:** Allowed to continue stable pain medication (including opioids) and asked not to make any changes to current dosages **Follow-up:** 4 weeks	**AEs:** Significantly more tramadol patients experienced 1 or more AEs compared with placebo (91% tramadol, 58% placebo, p=0.02). The most common AEs, reported by more than 5% of patients in either group, were tiredness, dry mouth, dizziness, sweating, constipation, and nausea. The potential significance of a between group difference was not reported. **Serious AEs:** Not reported **AEs Leading to Discontinuation:** Twelve patients withdrew from the study due to AE, of whom at least 11 were in the tramadol group. **AEs for Tramadol:** More than 5% of tramadol patients reported tiredness (74%), dry mouth (52%), dizziness (52%), sweating (39%), constipation (35%), nausea (39%). **Attrition:** Tramadol (48%), placebo (17%)

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Reference: Schiphorst Preuper et al 2014[13] **Country:** The Netherlands **Study Design:** Randomized controlled trial **Purpose:** To explore the effects of tramadol ER on functioning in chronic LBP **Quality Rating:** Good Intent-to-treat analyses. Triple blinding until final manuscript. Block randomization. Clinical and demographic characteristics between groups were not significantly different at baseline. Analgesic washout period. Overall attrition 14% (<20% for each group)	**Number of Patients:** 50 (25 tramadol, 25 placebo) **Diagnosis:** Chronic LBP **Age in Years (Median [IQR]):** 42.0 (35.5-50.5) tramadol, 44.0 (32.5-48.0) placebo **Gender:** Tramadol (72% female, 28% male), placebo (64% female, 36% male) **Inclusion Criteria:** Non-specific chronic LBP lasting >3 months, VAS for worst pain in the past week ≥4.0 cm, age >18 years, on the waiting list for rehabilitation treatment, willing to take the trial medication for 2 weeks **Exclusion Criteria:** Mental (e.g., major psychiatric disorders) or physical causes (e.g., cardiac or pulmonary disorders) leading to reduction in functioning, hypertension, unable/unsafe to participate in functional capacity evaluation, contraindication or known AE for prescribed medication, use of opioids, unwillingness to stop pain medication or other treatments for chronic LBP	**Tramadol/Acetaminophen Group:** 37.5 mg/375 mg bid to 75 mg/750 mg tid **Placebo Group:** Placebo (identical in packaging to tramadol) **Supplemental Analgesia:** None **Follow-up:** 2 weeks	**AEs:** Side effects were reported in 50% of the tramadol group and 24% of the placebo group and consisted of dizziness, nausea, tiredness, diarrhea, and a short period of skin rash. **Attrition:** 16% of patients in the tramadol group and 12% of patients in the placebo group discontinued the study after randomization and the first dose. Two patients in the tramadol group discontinued the study due to side effects (headache, diarrhea, nausea). **Lost to Follow-Up:** 4% in tramadol group due to family circumstances
Reference: Überall et al 2012[15] **Country:** Germany **Study Design:** Randomized controlled trial **Purpose:** To demonstrate non-inferior or superior efficacy of flupirtine modified release (MR) compared with tramadol ER and placebo for moderate to severe chronic LBP **Quality Rating:** Fair Intent-to-treat analysis. Double blind. Computer-generated allocation list with block randomization stratified by site. Analgesic washout period.	**Number of Patients:** 355 (119 flupirtine, 116 tramadol, 120 placebo) **Diagnosis:** Moderate-to-severe chronic LBP **Age in Years (Mean±SD):** 58.6±13.0 flupirtine, 57.6±12.4 tramadol, 58.5±12.1 placebo **Gender:** Flupirtine (68.9% female, 31.1% male), tramadol (61.2% female, 38.8% male), placebo (55.8% female, 44.2% male) **Inclusion Criteria:** Taking adequate analgesics for low back pain, dissatisfied with their current treatment, average baseline pain intensity either ≥4 on an 11-point numerical rating scale or at least moderate on a 5-point verbal rating scale **Exclusion Criteria:** Chronic LBP due to neurologic cause, recent major trauma, or a visceral disorder; clinically significant medical or	**Flupirtine MR Group:** 400 mg qd in the evening **Tramadol ER Group:** 200 mg qd in the evening **Placebo Group:** matching placebo qd in the evening **Supplemental Analgesia:** Patients received 50 mg diclofenac natrium tablets and were permitted to use up to 150 mg per day. Patients were instructed to use as little as possible and stop diclofenac therapy at least 24 hours before any clinic visit. **Follow-up:** 5 weeks	**TEAEs:** Significantly more tramadol ER patients experienced TEAEs than flupirtine patients (34.5% tramadol, 21.0% flupirtine, p=0.039) and significantly more tramadol patients experienced TEAEs than placebo (15.8% placebo, p=0.001). No significant between group difference was reported for flupirtine and placebo in number of patients with TEAEs. Patients in the tramadol group experienced TEAEs significantly sooner than patients in the flupirtine group (p<0.001) or the placebo group (p<0.001). The most common TEAEs, reported by more than 5% of patients in any single group, were nausea, dizziness, fatigue, and vomiting.

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Clinical and demographic characteristics between groups were well balanced at baseline. Attrition rate ≥20% for all groups.	psychiatric disease; history of rheumatoid arthritis, psoriasis, spondyloarthropathies or any other kind of chronic inflammatory disease with a possible involvement of the spinal column; metabolic bone disease; spinal stenosis (associated with neurological impairment); spinal fractures; anatomical deformities; malignancy; fibromyalgia; infections of the brain, spinal cord, or peripheral nerves; a herniated disc associated with neurological impairment; seizure disorder; alcohol/analgesic/narcotic or other substance abuse within the past 2 years as well as neurological or psychiatric disease which would either interfere with the subject's proper completion of the study or appropriate self-assessments; or exposure to another investigational agent within the last 30 days; history of spinal surgical interventions; lactating females or females of child-bearing potential not employing adequate contraception; renal or hepatic impairment and abnormal baseline laboratory values that might affect patient safety; contraindications and/or known hypersensitivity to flupirtine, tramadol, diclofenac or to excipients of their pharmaceutical preparations		**Nausea**: Significantly more tramadol patients (19.0%) experienced nausea compared with flupirtine (1.7%, p<0.001) and placebo (2.5%) (p=0.001 for tramadol vs. placebo; p<0.001 for flupirtine vs. placebo) **Vomiting**: Significantly more tramadol patients (11.2%) experienced vomiting compared with placebo (0.8%) or flupirtine 0%; p<0.001 for both comparisons) **Dizziness**: More tramadol (12.9%) patients experienced dizziness than flupirtine patients (6.0%; not significant). Significantly more tramadol patients experienced dizziness than placebo patients (3.3%; p=0.008). No significant between group differences were reported for this outcome for tramadol versus flupirtine. **Fatigue**: No significant between group differences were reported for fatigue in all groups. **Serious TEAEs:** No serious TEAEs were reported in any group. No deaths occurred during the study. **TEAEs Leading to discontinuation:** Significant between group differences were reported between tramadol vs. flupirtine (14 tramadol, 4 flupirtine, p=0.017) and tramadol vs. placebo (4 placebo, p=0.014) for number of patients who discontinued due to TEAEs. No significant between group difference was reported for flupirtine and placebo in number of patients who discontinued due to TEAEs. **TEAEs for Flupirtine MR:** The following TEAEs were reported in more than 5% of patients during the study period: dizziness (6.0%), fatigue (6.0%). **TEAEs for Tramadol ER:** The following TEAEs were reported in more than 5% of

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			patients during the study period: nausea (19.0%), dizziness (12.9%), fatigue (6.0%), vomiting (11.2%). **Attrition:** Flupirtine MR group (20.2%): 10 patients had major protocol deviation; 4 discontinued from study due to TEAEs, 8 due to non-compliance, 2 due to lack of efficacy. Tramadol ER group (26.7%): 9 patients had major protocol deviation; 14 discontinued from study due to TEAEs, 6 due to non-compliance, 1 due to lack of efficacy, 1 due to patient choice. Placebo group (20%): 10 patients had major protocol deviation; 4 discontinued from study due to TEAEs, 8 due to non-compliance, 2 due to lack of efficacy.

AE: adverse event; BTDS: buprenorphine transdermal delivery system; CR: controlled release; ER: extended release; IQR: interquartile range; LBP: low back pain; mg: milligram; MR: modified release; ms: millisecond; OLE: open label extension; qd: once daily; SCI: spinal cord injury; SD: standard deviation; TEAE: treatment emergent adverse events; tid: three times a day; VAS: visual analog scale

Appendix B. References

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Appendix C. Excluded Studies

Table 4. Excluded Studies

Reference	Reason for Exclusion
Phua et al. 2015[20]	A systematic review evaluating cohort and case-control study data
Trenkwalder et al. 2015[21]	Not a chronic pain population
Hauser et al. 2014[22]	Clinical practice guideline
Michna et al. 2014[23]	Most studies published prior to 2009
Schwartz et al. 2014[24]	Pooled analysis of studies[2,3] included in this report
Cloutier et al. 2013[25]	Duplicate of Cloutier[18]
Lee et al. 2013[26]	Case-control design
Suzan et al. 2013[27]	Not a comparative study
Haroutiunian et al. 2012[28]	3 primary studies do not meet inclusion criteria
Steiger et al. 2012[29]	Lacks a comparison group
Krebs et al. 2011[30]	Not a systematic review or randomized controlled trial
Manchikanti et al. 2011[31]	Most studies published prior to 2009
Buynak et al. 2010[32]	Included in 2015 Santos review[1]
Papaleontiou et al. 2010[33]	Only 1 study (Karlsson 2009) meets publication and study design criteria
Watson et al. 2010[34]	Relevant primary studies published prior to 2009
Nalamachu et al. 2009[35]	Description of planned trial, does not include outcomes data
Rauck et al. 2009[36]	Not a study population of interest

Key Question 5: What is the comparative effectiveness and safety of various opioid formulations?

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Key Question 5: What is the comparative effectiveness and safety of various opioid formulations?

Treatments to be considered for this key question include:

- Abuse deterrent formulations compared to non-abuse deterrent formulations
- Immediate-release/short-acting opioids compared to extended-release/long-acting opioids
- Route of administration/ delivery alternatives such as transdermal, buccal, sublingual, pumps
- Tramadol and other dual-mechanism opioids
- Buprenorphine
- Methadone

Summary of Evidence Base

Our searches identified two previously published systematic reviews (SRs) and 7 randomized controlled trials RCTs that examined the benefits and harms of different opioid formulations to address this key question. Both SRs and 3 individual trials considered the use of chronic opioid therapy (at least 12 weeks) in patients with chronic pain. For these papers we include outcomes related to both safety and efficacy. Four RCTs had less than 12 weeks follow-up and, per protocol for ECRI Institute's evidence synthesis, outcomes for safety only are included in this evidence report.

Long-term Trials

- Morphine vs. Other Opioids
    - One network meta-analysis[1] evaluated the appropriateness of using morphine as the reference standard for safety and efficacy of World Health Organization (WHO) Step III opioids (i.e., strong opioids) for treating chronic cancer or non-cancer pain. There were no differences in ratings of pain intensity between morphine and fentanyl, hydrocodone, or oxycodone (Quality of evidence: Low).
    - Low quality evidence suggests that there is no difference between morphine and other Step III opioids with respect to serious adverse events.
- Tapentadol
    - One SR[2] considered the efficacy, safety, and tolerability of tapentadol extended-release (ER) for moderate-to-severe chronic osteoarthritis or back pain. The evidence base consisted of 4 RCTs enrolling 4,094 patients and compared tapentadol extended-release to oxycodone controlled release or to placebo. The placebo data are considered in the chapter for Key Questions 3 and 4.
        - For the outcome of change in pain intensity, Moderate quality supports the use of tapentadol over oxycodone in patients with chronic pain.
        - Low quality evidence suggests that there is no difference between tapentadol and oxycodone with respect to serious adverse events.

- Moderate quality evidence supports the use of tapentadol over oxycodone for avoiding non-serious adverse effects or discontinuation of treatment due to adverse events.

- Abuse-deterrent Formulations
  - One open-label RCT[3] considered the safety and tolerability of an abuse-deterrent formulation of oxycodone/naloxone (OXN) relative to oxycodone (OXY) or morphine (MOR).
    - Pain relief was statistically significantly higher for patients receiving OXN than for those receiving OXY or MOR. There were no differences in pain relief between patients receiving OXY and MOR (Quality of evidence: Low to Very low).
    - Quality of life was statistically significantly improved for patients receiving OXN than for those receiving OXY or MOR. There were no differences in quality of life between patients receiving OXY and MOR (Quality of evidence: Low to Very low).
    - Opioid-induced constipation was statistically significantly improved for patients receiving OXN than for those receiving OXY or MOR. There were no differences in opioid-induced constipation between patients receiving OXY and MOR (Quality of evidence: Low to Very low).
    - Patients taking OXN were less likely to experience treatment related adverse events or to discontinue treatment due to adverse effects than patients taking OXY or MOR. There were no differences in treatment related adverse events or discontinuation between patients receiving OXY and MOR (Quality of evidence: Low to Very low).

- Buprenorphine
  - Two RCTs considered the use of transdermal buprenorphine in managing either chronic low back pain[4] or chronic osteoarthritis pain.[5]
    - One double-blind, double-dummy RCT[4] comparing high dose buprenorphine (BTDS 20: 20 mcg/h) or oxycodone (40 mg/d) to low dose buprenorphine (BTDS 5: 5 mcg/h) reported that pain was statistically significantly lower in patients receiving BTDS 20 or oxycodone than in patients receiving BTDS 5 (Quality of evidence: Low)
    - One open-label, non-inferiority RCT[5] comparing buprenorphine to tramadol reported that buprenorphine was non-inferior to tramadol for the outcome of pain relief (Quality of evidence: Very low).
    - One double-blind, double-dummy RCT[4] comparing BTDS 20 or oxycodone to low dose BTDS 5 reported that patients using BTDS 20 had statistically significantly lower sleep disturbance and lower supplemental analgesic medication use than patients using BTDS 5 (Quality of evidence: Low)
    - One double-blind, double-dummy RCT[4] comparing BTDS 20 or oxycodone to low dose BTDS 5 reported that patients using oxycodone did not differ in the outcomes of sleep disturbance or supplemental analgesic medication relative to patients using BTDS 5 (Quality of evidence: Very low)

Short-term Trials

- Abuse-deterrent Formulations
  - One RCT[6] considered the use of safety and efficacy of oxycodone/naloxone prolonged-release (OXN PR) relative to oxycodone prolonged-release (OXY PR). Opioid-induced constipation was significantly improved to a greater degree for patients receiving OXN PR relative to patients receiving OXY PR (Quality of evidence: Low to Very low).
- Buprenorphine: Transdermal vs. Sublingual
  - One RCT[7] considered the safety of low-dose transdermal buprenorphine relative to low-dose sublingual buprenorphine in patients with chronic osteoarthritis. Rates of adverse events were lower in patients receiving the transdermal formulation of buprenorphine relative to those receiving sublingual buprenorphine (Quality of evidence: Very low).
  - For the outcome of skin irritation, no differences were observed between patients receiving the active transdermal patch and the placebo transdermal patch, with the exception of redness during the titration phase. During titration, redness was more common for patients receiving active transdermal buprenorphine relative to those receiving placebo patches (Quality of evidence: Very low).
- Long-acting vs. Short-acting Formulations
  - Two RCTs[8,9] considered the safety of short-acting opioids and long-acting opioids in patients with chronic pain. One small RCT[8] compared long-acting (LA) dihydrocodeine to short-acting (SA) dihydrocodeine. The other RCT[9] compared hydromorphone extended release (ER) to twice-daily controlled-release oxycodone (CR). Both studies employed a double-blind, double-dummy design. Rates of adverse events were reported in both trials, but there were very serious concerns about lack of statistical analysis of the outcomes, small sample size in one trial, lack of precision in reporting data, and lack of statistical power. The evidence provided by these two trials may be too sparse to inform decision-making (Quality of evidence: Very low).

Overview of Evidence Base

Our searches identified two previously published systematic reviews (SRs)[1,2] and 6 randomized controlled trials (RCTs)[3-9] that examined the benefits and harms of different opioid formulations in treating adults with chronic pain. Systematic reviews and RCTs published on or after March 2009 were considered as evidence for this key question. RCTs that were included in the SRs were not included as individual studies. Studies excluded as evidence for this key question are presented in Table 4 of Appendices.

Both SRs[1,2] and 3 individual trials[3-5] considered the use of chronic opioid therapy (at least 12 weeks) in patients with chronic pain. For these papers we include outcomes related to both safety and efficacy. Four RCTs[5-8] had less than 12 weeks follow-up and, per protocol for ECRI Institute's evidence synthesis, outcomes for safety only are included in this evidence report. For clarity, the evidence for these studies is presented separately as long-term trials and short-term trials.

Long-term Trials

Morphine vs. Other Opioids: One network meta-analysis[1] evaluated the appropriateness of using morphine as the reference standard for safety and efficacy of World Health Organization (WHO) Step III opioids (i.e., strong opioids). The evidence base consisted of 56 RCTs comparing step III to placebo or to other step III opioids for treating chronic cancer or non-cancer pain.

Tapentadol: One SR[2] considered the efficacy, safety, and tolerability of tapentadol extended-release (ER) for moderate-to-severe chronic osteoarthritis or back pain. The evidence base consisted of 4 RCTs enrolling 4,094 patients and compared tapentadol extended-release to oxycodone controlled release or to placebo. The placebo data are considered in the chapter for Key Questions 3 and 4.

Abuse-deterrent Formulations: One open-label RCT[3] enrolling 453 patients with chronic low back pain considered the safety and tolerability of an abuse-deterrent formulation of oxycodone/naloxone (OXN) relative to oxycodone (OXY) or morphine (MOR).

Buprenorphine: Two RCTs enrolling 797 patients considered the use of transdermal buprenorphine in managing chronic low back pain[4] or chronic osteoarthritis pain.[5] The trial conducted in patients with chronic low back pain administered trial medications according to a double-blind, double-dummy scheme and used immediate-release oxycodone as the comparator.[4] The study conducted in patients with chronic osteoarthritis was designed as an open-label, non-inferiority trial and used tramadol as the comparator.[5]

Short-term Trials

Abuse-deterrent Formulations: One RCT[6] considered the use of safety and efficacy of oxycodone/naloxone prolonged-release (OXN PR) relative to oxycodone prolonged-release (OXY PR) in 184 patients with moderate to severe chronic cancer pain. The primary aims of this trial were to assess the impact of using OXN PR on opioid-induced constipation (OIC).

Buprenorphine: Transdermal vs. Sublingual: One RCT[7] considered the safety of low-dose transdermal buprenorphine relative to low-dose sublingual buprenorphine in 238 patients with chronic osteoarthritis. This study employed a double-blind, double-dummy design.

Long-acting vs. Short-acting Formulations: Two RCTs[8,9] considered the safety of short-acting opioids and long-acting opioids in patients with chronic pain. One small RCT[8] enrolling 58 patients with chronic non-malignant pain compared long-acting (LA) dihydrocodeine to short-acting (SA) dihydrocodeine. The other RCT[9] enrolled 260 patients with chronic cancer pain and compared hydromorphone extended release (ER) to twice-daily controlled-release oxycodone (CR). Both studies employed a double-blind, double-dummy design.

Study Quality Rating

The studies included in the SRs were rated overall as fair quality by the authors of the reviews.[1,2] Study limitations in the review by Bekkering et al.[1] included concerns about inadequate randomization, blinding, allocation concealment, and manufacturer funding source. Study limitations in the review by Santos et al.[2] included high risk of bias due to incomplete reporting of outcome data, and concerns regarding the outcomes selected, and lack of clarity regarding allocation concealment. See Table 2 for quality ratings for each review paper.

The study quality for the included individual trials[3-9] ranged from Fair to Poor using U.S. Preventive Services Task Force (USPSTF) criteria. Only one trial was rated as Fair,[6] and the remainder were rated as Poor.[3-5,7-9] The main study limitations were related to moderate to high participant attrition, lack of blinding or use of open label design, and potential reporting bias. Lack of blinding is a concern in trials assessing efficacy of pain medication as reporting of pain is subjective and is subject to expectation bias. See Table 3 for quality ratings for each individual study.

Evidence Base, Synthesis of Results and Quality of Evidence for Each Medication Comparison

Below we provide a brief description of key aspects of the study, patients, and interventions covered in the included studies, as well as treatment outcomes and quality of evidence. All patients had a primary diagnosis of chronic pain. In general, reporting of the rates of adverse events was not presented in a manner that enabled rating of the evidence; therefore, these data are described narratively where appropriate. Unless otherwise noted, most RCTs allowed use of some form of rescue medication during the study. Additional information on study, patient and intervention characteristics is provided in Table 2 (SRs) and Table 3 (RCTs). Additional information on quality of evidence appears in Table 1.

Long-term Studies

Morphine vs. Other Opioids

Study, Patient and Intervention Characteristics

One network meta-analysis[1] evaluated the appropriateness of using morphine as the reference standard for safety and efficacy of WHO Step III opioids. The evidence base consisted of 56 RCTs comparing step III to placebo or to other step III opioids for treating chronic cancer or non-cancer pain. This SR reported on trials of differing lengths, we focused on trials with mean follow-up of at least 12 weeks for inclusion in this evidence report. Enrollment in individual trials ranged from 21 patients to 684 patients but the total number of patients across all trials was not reported. The majority of the included trials for this evidence report enrolled patients aged between 20 and 90 years. The percentage of women enrolled in the included trials ranged from 27.5% to 74%.

Outcomes

Pain Intensity

Note that for this SR, a weighted mean difference (WMD) between treatment groups greater than 0 indicates that morphine is more effective than the comparator. There were no differences in ratings of pain intensity between morphine and fentanyl, hydrocodone, or oxycodone. Participants receiving morphine (given with naltrexone) had statistically significantly reduced pain intensity than those receiving placebo (WMD=11.1; 95% CI: 5.4 to 16.8).[1] Please see Tables 1 and 2 for complete description of comparators and outcomes.

Serious Adverse

There was no significant difference between treatment conditions on rates of serious adverse events (RR=1.15; 95% CI: 0.79 to 1.67), but the 95% CI is too wide to rule out the possibility of a difference.

Treatment Discontinuation

Within the SR, data for treatment discontinuation were stratified according to type of pain (cancer pain vs. non-cancer pain) and for reason for discontinuation (lack of efficacy or adverse events). Please see Tables 1 and 2 for complete description of comparators and outcomes.

For patients with cancer pain (10 studies; n=1,047), there were no differences between treatment comparisons for patients discontinuing due to a lack of treatment efficacy. For discontinuation due to adverse events, however, comparisons between morphine and placebo or methadone favored morphine. In these comparisons patients were more likely to drop out if they had been given methadone (OR=3.00; 95% CI: 1.11 to 8.11). In contrast, patients receiving fentanyl were less likely to drop out due to adverse events than patients receiving morphine (OR=0.12; 95% CI: 0.04 to 0.36). Comparisons for hydromorphone and oxycodone were not significant.

For patients with non-cancer pain (27 studies; n=8,177), more patients were likely to discontinue due to a lack of treatment efficacy if they received placebo (OR=3.71; 95% CI: 2.27 to 6.08) or buprenorphine (OR=2.37; 95% CI: 1.32 to 4.28). Comparisons for fentanyl, hydromorphone, oxycodone, and oxymorphone were not significant. For discontinuation due to adverse events, comparisons for placebo (OR=0.13; 95% CI: 0.08 to 0.21), buprenorphine (OR=0.49; 95% CI: 0.24 to 0.99), and fentanyl (OR=0.41; 95% CI: 0.19 to 0.87) favored the comparator. In these comparisons patients were more likely to drop out if they had been given morphine. Comparisons for hydromorphone, oxycodone, and oxymorphone were not significant.

Quality of Evidence Rating

The quality of evidence ratings for the evidence presented in the SR by Bekkering et al.[1] ranged from Moderate to Low across different outcomes (See Table 1). Moderate quality ratings reflected the limitations of using a large SR with a Fair evidence base, with no further concerns regarding consistency, directness, or precision. Additional concerns regarding serious imprecision in the treatment effect estimate resulted in a further downgrade of the evidence for some outcomes to Low. For the outcome of pain intensity, Low quality evidence does not support the use of other Step III opioids over morphine in patients with chronic pain. This does not mean the other opioids lack efficacy, just that the differences in efficacy compared to morphine are very small or nonexistent. Moderate quality supports the use of morphine over placebo in patients with chronic pain. Low quality evidence suggests that there is no difference between morphine and other Step III opioids with respect to serious adverse events. Moderate to Low quality evidence supports the use of different treatments in different patient populations for avoiding discontinuation of treatment due to either lack of efficacy or adverse events (See Table 1). Taken together these findings suggest that while pain relief may be similar across treatment with different opioids, there are individual patient and medication-specific factors that may influence retention in pain management treatment.

Tapentadol

Study, Patient and Intervention Characteristics

One SR by Santos et al.[2] considered the efficacy, safety, and tolerability of tapentadol ER for moderate-to-severe chronic osteoarthritis or back pain. The evidence base consisted of 4 RCTs enrolling 4,094 patients and compared tapentadol extended-release to oxycodone controlled release. When reported, mean patient

age was approximately 40 years. Gender was not reported. The studies compared tapentadol ER (100 to 250 mg/day) to oxycodone CR (20 to 50 mg/day). Minimum follow-up was 12 weeks.

Outcomes

Change in Pain Intensity from Baseline

Data analysis for this SR[2] did not compare pain levels between treatment conditions at the end of the trials but compared the change relative to baseline. Patients taking tapentadol had statistically significantly greater reductions in pain intensity from baseline relative to patients taking oxycodone (Mean difference [MD] = -0.24; 95% CI: -0.43 to -0.05).

Serious Adverse

There was no significant difference between treatment conditions on rates of serious adverse events (RR=0.57; 95% CI: 0.24 to 1.33), but the 95% CI is too wide to rule out the possibility of a difference.[2]

Treatment Discontinuation

Patients taking tapentadol were less likely to experience adverse effects of treatment (RR=0.91; 95% CI: 0.85 to 0.96) or to discontinue treatment due to adverse effects (RR=0.50; 95% CI: 0.42 to 0.60) than patients taking oxycodone.[2]

Quality of Evidence Rating

The quality of evidence ratings for the evidence presented in the SR by Santos et al.[2] ranged from Moderate to Low across different outcomes (See Table 1). Moderate quality ratings reflected the limitations of using a large SR with a Fair evidence base, with no further concerns regarding consistency, directness, or precision. Additional concerns regarding serious imprecision in the treatment effect estimate resulted in a further downgrade of the evidence for some outcomes to Low. For the outcome of change in pain intensity, Moderate quality supports the use of tapentadol over oxycodone in patients with chronic pain. Low quality evidence suggests that there is no difference between tapentadol and oxycodone with respect to serious adverse events. Moderate quality evidence supports the use of tapentadol over oxycodone for avoiding non-serious adverse effects or discontinuation of treatment due to adverse events (See Table 1).

Abuse-deterrent Formulations

Study, Patient and Intervention Characteristics

One open-label RCT[3] enrolling 453 patients with chronic low back pain considered the safety and tolerability of an abuse-deterrent formulation of OXN relative to OXY or MOR. Patients were approximately 46 years of age and 43.7% were male. For opioid-naïve patients, the recommended starting dose was 20 mg morphine equivalent (MEQ) for prolonged release treatments. Dose adjustments were made at the discretion of the physician. Medications were prescribed by participating physicians and were not provided by the investigators. Use of rescue medication was permitted at the physician's discretion. Follow-up was 12 weeks.

Outcomes

Pain was assessed using the modified Pain Disability Index (mPDI), the German Pain Diary, and the Low back pain intensity index (LBPIX). Quality of life was assessed using the Quality of life (QOL) impairment

by pain (QLIP) index. Treatment emergent adverse events (TEAEs) were monitored, and opioid-induced constipation (OIC) was assessed using the bowel-function index (BFI).[3]

Pain Relief

Pain relief, defined as improvements of at least 50% from baseline for mPDI and LBPIX, was statistically significantly higher for patients receiving OXN than for those receiving OXY (mPDI: OR=1.64; 95% CI: 1.03 to 2.60; p<0.001; LBPIX: OR=2.09; 95% CI: 1.27 to 3.44; p<0.001) or MOR (mPDI: OR=1.83; 95% CI: 1.16 to 2.89; p<0.001; LBPIX: OR=2.71; 95% CI: 1.66 to 4.42; p<0.001). There were no significant differences in pain relief between patients receiving OXY and MOR (mPDI: OR=1.12; 95% CI: 0.72 to 1.75; p=0.36; LBPIX: OR=1.30; 95% CI: 0.83 to 2.04; p=0.19), but the 95% CIs were too wide to rule out the possibility of a difference.[3]

QoL

Improvements in QoL were defined as at least 50% improvement from baseline. QoL was statistically significantly improved for patients receiving OXN than for those receiving OXY (OR=2.07; 95% CI: 1.30 to 3.31; p<0.001) or MOR (OR=2.50; 95% CI: 1.57 to 3.99; p<0.001). There were no significant differences in QoL between patients receiving OXY and MOR (OR=1.21; 95% CI: 0.77 to 1.89; p=0.15.), but the 95% CI is too wide to rule out the possibility of a difference.[3]

OIC

Improvements in OIC were defined as having less than a 50% increase in BFI scores from baseline. OIC was statistically significantly improved for patients receiving OXN than for those receiving OXY (OR=2.41; 95% CI: 1.45 to 3.99; p<0.001) or MOR (OR=2.75; 95% CI: 1.67 to 4.52; p<0.001). There were no significant differences in OIC between patients receiving OXY and MOR (OR=1.14; 95% CI: 0.73 to 1.79; p=0.30), but the 95% CI does not rule out the possibility of a difference.[3]

Adverse

There were no serious adverse events reported. The most commonly reported TEAEs were: Constipation, nausea, somnolence, dizziness, and sleep problems. Statistically significantly fewer patients taking OXN reported experiencing at least one TEAE than patients taking OXY (OR=2.41; 95% CI: 1.35 to 4.31); The difference favoring OXN versus MOR did not reach statistical significance (OR=1.79; 95% CI: 0.99 to 3.24).[3]

TEAE Treatment Discontinuation

Patients taking OXN were less likely to discontinue treatment due to adverse effects than patients taking OXY (OR=2.28; 95% CI: 1.20 to 4.32; p<0.001) or MOR (OR=2.79; 95% CI: 1.48 to 5.26; p<0.001). There were no significant differences in treatment discontinuation for patients taking MOR or OXY (OR=1.22; 95% CI: 0.73 to 2.07; p=0.22), although the 95% CI is too wide to rule out the possibility of a difference.[3]

Quality of Evidence Rating

The quality of evidence ratings for the evidence presented in the RCT by Ueberall[3] ranged from Low to Very low across different outcomes (See Table 1). Low quality ratings reflected the limitations of using a Poor RCT, with no further concerns regarding consistency, directness, or precision. Additional concerns

regarding serious imprecision in the treatment effect estimate resulted in a further downgrade of the evidence for some outcomes to Very low. For the outcomes of change in pain intensity, QoL, OIC, and adverse events, Low quality evidence supports the use of OXN over either OXY or MOR in patients with chronic pain. For the outcomes of change in pain intensity, QoL, OIC, and adverse events, Very low quality evidence supports the use of OXY over MOR in patients with chronic pain (See Table 1).

Buprenorphine

Study, Patient and Intervention Characteristics

Two RCTs enrolling 797 patients considered the use of transdermal buprenorphine in managing chronic low back pain[4] or chronic osteoarthritis pain.[5] The trial by Steiner et al.[4] enrolled 662 patients with chronic low back pain. Patients were approximately 50 years of age and about half of the patients were male. Trial medications (buprenorphine transdermal system [BTDS] 7-day patch) were given according to a double-blind, double-dummy scheme and used immediate-release oxycodone as the comparator. There were three treatment conditions: BTDS 5: 5 mcg/h buprenorphine; BTDS 20: 20 mcg/h buprenorphine; Oxycodone: 2 5–mg immediate-release oxycodone capsules given every 6h total dose 40 mg/day). Use of rescue medication was permitted, but use within 24-h prior to pain assessments rendered that day's pain score as invalid. Data for that day were interpolated using 2 adjacent valid pain scores[4] The study by Karlsson et al.[5] enrolled 135 patients with chronic osteoarthritis. Patients were aged approximately 64.3 years, and most participants were female (29% male). The trial was designed as an open-label, non-inferiority trial and used tramadol as the comparator. Use of paracetamol as a rescue medication was permitted throughout the trial.[5] Follow-up in both trials was 12 weeks.

Outcomes

Pain was assessed using a score of "Average pain over the last 24 hours"[4] or a Box Scale 11 (BS-11) score.[5] Steiner et al.[4] also reported on disability as measured by the Oswestry Disability Index (ODI); Sleep Disturbance as measured by the Medical Outcome Study (MOS)-Sleep and use of supplemental pain medication. Although Karlsson et al.[5] described use of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, the EuroQol EQ-5D health states index, and the EuroQol visual analog scale (EQ-VAS), scores for these measures were not presented and thus were not included in this evidence report. For both trials, rates of adverse events were reported to be similar between groups and the most commonly reported adverse events were nausea, constipation, dizziness, pain, and fatigue. Steiner et al. report narratively on adverse events related to substance misuse. Rates of these events were low, but the narrative is presented as substance misuse is of direct relevance to this report:

> "Three SAEs were related to drug abuse. Cocaine abuse was recorded as an SAE for the patient who died during the run-in period. Oxycodone abuse during the double-blind phase was recorded as an SAE for a second patient who completed the study. Hydrocodone/acetaminophen abuse during the double-blind phase was recorded as an SAE for a third patient whose abuse of this non-protocol specified medication had been discovered after the patient had completed the study. Additionally, a patient who was receiving BTDS 5 in the double-blind phase discontinued from the study due to an SAE that was associated with suspected BTDS abuse."[4]

Steiner et al. also note:

> "The primary treatment comparison was between the BTDS 20 and BTDS 5 treatment groups and only used data observed while patients were exposed to study drug. Comparison between the BTDS 5 and the oxycodone 40 mg/day treatment groups was conducted to evaluate the assay sensitivity of the study. The study was not sized to detect differences between BTDS 20 and oxycodone 40 mg/day."[4]

Pain Relief

Steiner et al.[4] found that pain was statistically significantly lower for patients receiving BTDS 20 (Difference over weeks 4, 8, and 12: - 0.67 95% CI: -0.99 to -0.35) or oxycodone (Difference over weeks 4, 8, and 12: -.075; 95% CI: -1.07 to -0.44) relative to patients receiving BTDS 5.

Karlsson et al.[5] found that changes in pain from baseline were non-inferior for transdermal buprenorphine in comparison to tramadol (BS-11: Change from baseline: Buprenorphine: Least squares mean [LSM]: -2.26; 95% CI: -2.76 to -1.76; Tramadol: LSM: -2.09; 95% CI: -2.61 to -1.58).

Disability Scores

ODI scores did not vary between treatment conditions (BTDS 20 vs. BTDS 5: Treatment difference:-1.72; 95% CI: -3.55 to 0.11; Oxycodone vs. BTDS 5: Treatment difference:-1.99; 95% CI: -3.79 to -0.18).[4]

Sleep Disturbance

Patients receiving BTDS 20 had statistically significantly lower sleep disturbance than patients receiving BTDS 5 (Treatment difference: -6.23; 95% CI: -9.64 to -2.82; $p<0.001$). Sleep disturbance did not differ between patients receiving oxycodone and BTDS 5 (Treatment difference:-2.65; 95% CI: -6.01 to 0.70).[4]

Supplemental Analgesic Medication

Patients receiving BTDS 20 used statistically significantly less rescue medication than patients receiving BTDS 5 (Treatment difference: -0.50; 95% CI: -0.90 to -0.13; $p=0.006$). There were no differences between BTDS 5 and oxycodone in use of rescue medication (Treatment difference:-0.30; 95% CI: -0.70 to 0.09).[4]

Quality of Evidence Rating

The quality of evidence ratings for the evidence presented in the RCT by Steiner et al.[4] ranged from Low to Very low across different outcomes (See Table 1). Low quality ratings for outcomes reported in Steiner reflected the serious limitations of using a Poor RCT with no further concerns regarding consistency, directness, or precision. Additional concerns regarding serious imprecision in the treatment effect estimate resulted in a further downgrade of the evidence for some outcomes to Very low. For the outcome of pain over the previous 24 hours, Low quality evidence supports the use of either BTDS 20 or Oxycodone over BTDS 5. For the outcome of sleep disturbance, Low quality evidence supports the use of BTDS 20 over BTDS 5; Very low quality evidence does not support the use of Oxycodone over BTDS 5 in patients with chronic pain. For the outcome of reduced supplemental analgesic use, Low quality evidence supports the use of BTDS 20 over BTDS 5 and Very low quality evidence does not support the use of Oxycodone over BTDS 5 in patients with chronic pain.

Very low quality ratings for outcomes reported in Karlsson et al.[5] reflected the very serious limitations of using a Poor RCT, with serious imprecision due to the evidence base consisting of a single, small trial. For the outcomes of change in pain Very low quality evidence supports the use of buprenorphine in lieu of tramadol in patients with chronic pain (See Table 1).

Short-term Studies

Abuse-deterrent Formulations

Study, Patient and Intervention Characteristics

One RCT[6] considered the use of safety and efficacy of OXN PR relative to OXY PR in 184 patients with moderate to severe chronic cancer pain. Patients were approximately 64 years old and about half were male. Both OXN PR and OXY PR were given up to 120 mg/d. Oxycodone immediate-release was available as rescue medication, with a maximum of six doses per 24 h. Follow-up was 4 weeks.

Outcomes

Safety and adverse events were measured using the BFI, the Patient Assessment of Constipation Symptoms (PAC-SYM).

Constipation

Scores for the BFI and PAC-SYM significantly improved to a greater degree for patients receiving OXN PR relative to patients receiving OXY PR (BFI: Change in BFI = -11.14; 95% CI: -19.03 to -3.24; $p<0.01$; PAC-SYM total symptom score: $p=0.014$; frequency of symptoms: $p<0.01$).[6]

Adverse

Approximately 20% of AEs reported in this trial were related to cancer progression. 18 patients (10%) died during the 4-week trial: progression of malignant disease n=16; cardiac disorders: n=2. Rates of adverse events did not vary statistically between the two treatment conditions. The most commonly reported advents were related to GI function (e.g., nausea, vomiting, abdominal pain) and "general disorders and administration site conditions."

Note: there is lack of clarity regarding the definition of "administration site conditions." Medications were provided in tablets and taken *per os*.

Quality of Evidence Rating

The quality of evidence ratings for the evidence presented in the RCT by Ahmedzai et al.[6] ranged from Low to Very low for the outcomes related to constipation (See Table 1). Low quality ratings for change in BFI scores reflected the serious limitations of using a Fair RCT, with serious imprecision due to the evidence base consisting of a single, small trial. Ratings of Very low for change in PAC-SYM scores reflected an additional downgrade of the evidence due to serious imprecision around the effect estimate. For the outcomes of constipation Low to Very low evidence supports the use of OXN PR over OXY PR in a trial with follow-up of 4 weeks (See Table 1).

Buprenorphine: Transdermal vs. Sublingual

Study, Patient and Intervention Characteristics

One RCT[7] considered the use of safety and efficacy of low-dose transdermal buprenorphine relative to low-dose sublingual buprenorphine in 238 patients with chronic osteoarthritis. Patients were approximately 64.3 years old and 43.5% were male. Transdermal buprenorphine (5 to 20 mcg/hr) and sublingual buprenorphine (200 to 400 mcg/tablets) were administered according to a double-blind, double-dummy procedure. Oral paracetamol (500 mg) was permitted up to a maximum daily dose of 4,000 mg per day). Follow-up was up to 7 weeks.

Outcomes

Adverse

Significantly fewer patients receiving transdermal buprenorphine patches experienced adverse drug reactions relative to those receiving sublingual buprenorphine (Transdermal: 96 patients [81%]; Sublingual: 110 patients [92%]; p=0.0197). The most commonly reported adverse effects were: nausea, dizziness, vomiting, somnolence, headache, and asthenia. Rates of nausea (p=0.035), dizziness (p=0.026), and vomiting (p=0.039) were statistically significantly lower in patients given transdermal buprenorphine patches relative to those given sublingual buprenorphine.

Skin irritation as indicated by irritation and swelling did not vary statistically between the two treatment conditions. Patients reported that skin reactions were mild to moderate. Redness was more common during the titration phase of the trial for patients receiving active transdermal buprenorphine relative to those receiving placebo patches (p=0.016).

Quality of Evidence Rating

The quality of evidence ratings for the evidence presented in the RCT by James et al.[7] was Very low for all outcomes (See Table 1). Very low quality ratings reflected the very serious limitations of using a Poor RCT, with very serious imprecision due to the evidence base consisting of a single, small trial and serious imprecision in statistical reporting. For the outcomes of adverse events Very low evidence supports the use of transdermal buprenorphine over sublingual buprenorphine in a trial with follow-up of approximately 7 weeks (See Table 1).

Long-acting vs. Short-acting Formulations

Study, Patient and Intervention Characteristics

Two RCTs[8,9] considered the safety of short-acting opioids and long-acting opioids in patients with chronic pain. One small RCT[8] enrolled 58 patients with chronic non-malignant pain and compared LA dihydrocodeine to SA dihydrocodeine. Patients were approximately 46 years old and about 46% were male. An individual's dose of dihydrocodeine was given in comparable dose levels as pre-study codeine intake (LA dihydrocodeine: 120 to 240 mg/d given every 8 to 12 hr, with placebo [for SA] and paracetamol given 4 x per day; SA dihydrocodeine: 120 to 240 mg/d and paracetamol given 4 x per day, with placebo [for LA] taken 2 x per day). All patients received paracetamol in addition to dihydrocodeine. Paracetamol dose was given based on pre-study intake (Range: 2 to 4 g/d). Rescue medication was not permitted during the trial.

The other RCT[9] enrolled 260 patients with chronic cancer pain and compared hydromorphone ER to twice-daily CR oxycodone. Patients were approximately 53.1 years old and most were male (65.3%). ER hydromorphone (8 or 16 mg) was given once daily, with placebo (for CR and ER) given twice per day. CR oxycodone (10, 20, or 40 mg) was given twice a day, with placebo (for ER) taken twice per day. Use of morphine immediate release (IR) was permitted as a rescue medication (5 or 10 mg). Adjuvant medications were permitted if the patients were on a stable dose that needed to be maintained.

Both studies employed a double-blind, double-dummy design. Follow-up for Pedersen[8] was 8 weeks and for Yu[9] was 4 weeks.

Adverse

In Pedersen et al.,[8] the authors note that the study was not powered to assess adverse , and there was no statistical comparison between the groups. There were 36 adverse events in the LA dihydrocodeine condition and 22 events in the SA dihydrocodeine condition. The most frequently reported adverse events were constipation, headache, and fatigue.

In Yu et al.,[9] there were 111 adverse events in the hydromorphone ER condition and 117 in the oxycodone CR condition. The most frequently reported adverse events were constipation, headache, and fatigue. The top ten most common TEAEs were vomiting, constipation, nausea, pyrexia, dizziness, decreased appetite, decreased white blood cell count, anemia, decreased appetite, and diarrhea.

Quality of Evidence Rating

The quality of evidence ratings for the evidence presented in the RCTs by Pedersen et al.[8] and Yu et al.[9] were Very low (See Table 1). Very low quality ratings for adverse events reflected the very serious limitations of using Poor RCTs, with very serious imprecision due to numerous limitations including lack of statistical analysis, small sample size,[8] lack of precision in reporting data, and lack of statistical power (See Table 1). The evidence provided by these two trials may be too sparse to inform decision-making.

Overall Quality of Evidence Rating

The overall quality of the evidence was assessed for each outcome using the GRADE system, which assigns a rating of High, Moderate, Low or Very low. By default, RCTs start at High quality of evidence and observational intervention studies start at Low quality of evidence. The evidence is then assessed for potential deficiencies in four primary domains: overall study quality (usually the average or median quality of individual studies for each outcome), indirectness (of interventions, study populations, outcomes, and/or comparisons), inconsistency (in direction and/or magnitude of effect) and imprecision (uncertainty in the estimate of effect due to variance or low sample size). Deficiencies in any of these domains may result in downgrading the quality of evidence by one or two levels. In instances where inconsistency in observed findings was related to imprecision, we did not downgrade further for inconsistency.

Table 1. Overall Assessment of Quality of Evidence Base

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Systematic Reviews and Trials Lasting at Least 12 Weeks								
Morphine Versus Other Opioids								
Pain intensity	1 SR (Bekkering et al. 2011[1])	Morphine vs. placebo Placebo 3–5 months; non-cancer pain Compared to morphine + naltrexone: morphine dose = 40 to 160 mg/d 1 study; n=344	Placebo 3-5 months; non-cancer pain Compared to morphine + naltrexone: morphine dose = 40 to 160 mg/d WMD=11.1; 95% CI: 5.4 to 16.8; **Favors morphine**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
	1 SR (Bekkering et al. 2011[1])	Morphine vs. fentanyl Fentanyl 12–24 months; 57 mcg/hr; non-cancer pain Morphine dose = 140 mg/d 1 study; n=680	WMD=1.0; 95% CI: −32.6 to 34.6; **Difference not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
	1 SR (Bekkering et al. 2011[1])	Morphine vs. Hydromorphone 2–5 months; 12-108 mg/d; cancer pain 1 study; n=200	WMD=6.7; 95% CI: −0.1 to 13.5; **Difference not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
	1 SR (Bekkering et al. 2011[1])	Morphine vs. Oxycodone 2–11 months; 34–84.7 mg/d; non-cancer pain Morphine dose = 30 to 78.7 mg/d 2 studies; n=489	WMD=3.9; 95% CI: −1.4 to 9.2; **Difference not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Serious adverse	1 SR (Bekkering et al. 2011[1])	Morphine vs. Other Step III opioids 3 studies	RR=1.15; 95% CI: 0.79 to 1.67. Not significant. There was no difference between treatment conditions on rates of serious adverse	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
Discontinuation due to adverse effects	1 SR (Bekkering et al. 2011[1])	Morphine vs. Other Step III opioids **Cancer pain** 10 studies; n=1,047	Morphine vs. Placebo OR=6.27; 95% CI: 0.74 to 53.12 **Not significant.**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Fentanyl OR=0.12; 95% CI: 0.04 to 0.36**; Favors fentanyl**. Patients receiving fentanyl were less likely to drop out due to adverse events than patients receiving morphine	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
			Morphine vs. Hydromorphone OR=1.46; 95% CI: 0.64 to 3.36 **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Methadone OR=3.00; 95% CI: 1.11 to 8.11 **Favors morphine**. Patients receiving methadone were more likely to drop out due to adverse events than patients receiving morphine.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
			Morphine vs. Oxycodone OR=0.51; 95% CI: 0.12 to 2.17 **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Discontinuation due to lack of efficacy	1 SR (Bekkering et al. 2011[1])	Morphine vs. Other Step III opioids **Cancer pain** 10 studies; n=1,047	Morphine vs. Placebo OR=1.88; 95% CI: 0.43 to 8.20	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Buprenorphine OR=0.48; 95% CI: 0.07 to 3.14	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Fentanyl OR=1.20; 95% CI: 0.39 to 3.65	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Hydromorphone OR=3.03; 95% CI: 0.93 to 9.87	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Methadone OR=0.89; 95% CI: 0.31 to 2.54	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Oxycodone OR=1.09; 95% CI: 0.07 to 17.8	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
Discontinuation due to adverse effects	1 SR (Bekkering et al. 2011[1])	Morphine vs. Other Step III opioids **Non-cancer pain** 27 studies; n=8,177	Morphine vs. Placebo OR=0.13; 95% CI: 0.08 to 0.21 **Favors placebo** Patients receiving placebo were less likely to drop out due to adverse events than patients receiving morphine	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
			Morphine vs. Buprenorphine OR=0.49; 95% CI: 0.24 to 0.99 **Favors buprenorphine** Patients receiving buprenorphine were less likely to drop out	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
			due to adverse events than patients receiving morphine					
			Morphine vs. Fentanyl OR=0.41 ; 95% CI: 0.19 to 0.87 **Favors fentanyl** Patients receiving fentanyl were less likely to drop out due to adverse events than patients receiving morphine	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
			Morphine vs. Hydromorphone OR=0.77; 95% CI: 0.44 to 1.35 **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Oxycodone OR=0.92; 95% CI: 0.58 to 1.49 **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Oxymorphone OR=0.78; 95% CI: 0.40 to 1.51 **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
Discontinuation due to lack of efficacy	1 SR (Bekkering et al. 2011[1])	Morphine vs. Other Step III opioids **Non-cancer pain** 27 studies; n=8,177	Morphine vs. Placebo OR=3.71; 95% CI: 2.27 to 6.08 **Favors morphine** Patients receiving placebo were more likely to drop out due to lack of efficacy than patients receiving morphine.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
			Morphine vs. Buprenorphine OR=2.37; 95% CI: 1.32 to 4.28 **Favors morphine** Patients receiving buprenorphine were more likely to drop out due to lack of efficacy than patients receiving morphine.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
			Morphine vs. Fentanyl OR=0.82 ; 95% CI: 0.48 to 1.40 **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Hydromorphone OR=0.94; 95% CI: 0.51 to 1.74 **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Oxycodone OR=0.71; 95% CI: 0.43 to 1.16 **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
			Morphine vs. Oxymorphone OR=0.73; 95% CI: 0.39 to 1.39 **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
Tapentadol								
Chance in pain intensity from baseline	1 SR (Santos et al. 2015[2])	Tapentadol extended-release vs. Oxycodone controlled release 4 studies; total n=3,116	MD=-0.24 95% CI: -0.43 to -0.05. **Favors tapentadol**. Patients taking tapentadol had greater reductions in pain intensity from baseline relative to patients taking oxycodone.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Efficacy in responders (those at least 50% pain reduction)	1 SR (Santos et al. 2015[2])	Tapentadol extended-release vs. Oxycodone controlled release Efficacy in responders. 2 studies; n=1,327	RR=1.46; 95% CI: 0.92, 2.32. **Not significant**.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low
Serious adverse	1 SR (Santos et al. 2015[2])	Tapentadol extended-release vs. Oxycodone controlled release 4 studies; n=3,099	RR=0.57; 95% CI: 0.24 to 1.33. **Not significant**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Adverse effects	1 SR (Santos et al. 2015[2])	Tapentadol extended-release vs. Oxycodone controlled release 3 studies; n=2,499	RR=0.91; 95% CI: 0.85 to 0.96. **Favors tapentadol** Patients taking tapentadol were less likely to experience adverse effects of treatment than patients taking oxycodone.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Discontinuation due to adverse effects	1 SR (Santos et al. 2015[2])	Tapentadol extended-release vs. Oxycodone controlled release 4 studies; n=3,102	RR=0.50; 95% CI: 0.42 to 0.60. **Favors tapentadol** Patients taking tapentadol were less likely to discontinue treatment due to adverse effects than patients taking oxycodone	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Abuse-deterrent Formulations								
Pain relief: mPDI ≥50% improvement from baseline	1 RCT (Ueberall and Mueller-Schwefe 2015[3])	**Number of Patients:** 453 OXN: n=144 OXY: n=151 MOR: n=158 **Initial Starting Dose**: Mean (SD) MEQ OXN: 29.3 (10.2) mg OXY: 28.9 (10.3) mg MOR: 29.8 (11.7) mg **Study Completion Dose**: Mean (SD) MEQ OXN: 124.1 (25.3) mg OXY: 120.0 (29.7) mg MOR: 126.7 (26.1) mg	OXY vs. OXN**:** OR=1.64; 95% CI: 1.03 to 2.60; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXN**:** OR=1.83; 95% CI: 1.16 to 2.89; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXY**:** OR=1.12; 95% CI: 0.72 to 1.75; p=0.36. Not significant	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Pain relief LBPIX ≥50% improvement from baseline	1 RCT (Ueberall and Mueller-Schwefe 2015[3])	**Number of Patients:** 453 OXN: n=144 OXY: n=151 MOR: n=158	OXY vs. OXN: OR=2.09; 95% CI: 1.27 to 3.44; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXN: OR=2.71; 95% CI: 1.66 to 4.42; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXY**:** OR=1.30; 95% CI: 0.83 to 2.04; p=0.19. Not significant.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low
QoL ≥50% improvement from baseline	1 RCT (Ueberall and Mueller-Schwefe 2015[3])	**Number of Patients:** 453 OXN: n=144 OXY: n=151 MOR: n=158	OXY vs. OXN**:** OR=2.07; 95% CI: 1.30 to 3.31; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXN: OR=2.50; 95% CI: 1.57 to 3.99; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXY**:** OR=1.21; 95% CI: 0.77 to 1.89; p=0.15. Not significant	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low
BFI Increase <50% from baseline	1 RCT (Ueberall and Mueller-Schwefe 2015[3])	**Number of Patients:** 453 OXN: n=144 OXY: n=151 MOR: n=158	OXY vs. OXN: OR=2.41; 95% CI: 1.45 to 3.99; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXN: OR=2.75; 95% CI: 1.67 to 4.52; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXY: OR=1.14; 95% CI: 0.73 to 1.79; p=0.30. Not significant	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low
Adverse	1 RCT (Ueberall and Mueller-Schwefe 2015[3])	**Number of Patients:** 453 OXN: n=144 OXY: n=151 MOR: n=158	OXN vs. OXY: OR=2.41; 95% CI: 1.35 to 4.31. **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			OXN vs. MOR: OR=1.79; 95% CI: 0.99 to 3.24. **Not significant**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
TEAE-related treatment discontinuations	1 RCT (Ueberall and Mueller-Schwefe 2015[3])	**Number of Patients:** 453 OXN: n=144 OXY: n=151 MOR: n=158	OXY vs. OXN**:** OR=2.28; 95% CI: 1.20 to 4.32; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXN: OR=2.79; 95% CI: 1.48 to 5.26; p<0.001; **Favors OXN**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			MOR vs. OXY**:** OR=1.22; 95% CI: 0.73 to 2.07; p=0.22. Not significant	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Very serious imprecision (-1)	Very low
Buprenorphine (Transdermal)								
Buprenorphine Versus Oxycodone								
Average pain over the previous 24 hours	1 RCT (Steiner et al. 2011[4])	BTDS 5 mcg/h: n=221 BTDS 20 msg/h: n=219 Oxycodone 40 mg/d: n=220	**BTDS 5 vs. BTDS 20** Difference from BTDS 5 over weeks 4,8, and 12: -0.67 95% CI: -0.99 to -0.35 Pain was statistically significantly lower for patients receiving BTDS 20 relative to patients receiving BTDS 5. **Favors BTDS 20**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			BTDS 5 vs. Oxycodone Difference from BTDS 5 over weeks 4,8, and 12: -.075; 95% CI: -1.07 to -0.44 Pain was statistically significantly lower for patients receiving oxycodone relative to patients receiving BTDS 5. **Favors Oxycodone**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Sleep disturbance	1 RCT (Steiner et al. 2011[4])	BTDS 5 mcg/h: n=221 BTDS 20 msg/h: n=219 Oxycodone 40 mg/d: n=220	**BTDS 20 versus BTDS 5** MOS sleep disturbance subscale: Treatment difference:-6.23; 95% CI: -9.64 to -2.82; p<0.001 **Favors BTDS 20**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
			Oxycodone 40 mg/day versus BTDS 5 MOS sleep disturbance subscale: Treatment difference:-2.65; 95% CI: -6.01 to-0.70 **Not significant**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low
Disability	1 RCT (Steiner et al. 2011[4])	BTDS 5 mcg/h: n=221 BTDS 20 msg/h: n=219 Oxycodone 40 mg/d: n=220	**BTDS 20 versus BTDS 5** ODI score: Treatment difference:-1.72; 95% CI: -3.55 to 0.11 **Not significant**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low
			Oxycodone 40 mg/day versus BTDS 5 ODI score: Treatment difference:-1.99; 95% CI: -3.79 to -0.18 **Not significant according to stepwise gate-keeping analysis α-level .05/3**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low
Supplemental analgesic medication	1 RCT (Steiner et al. 2011[4])	BTDS 5 mcg/h: n=221 BTDS 20 msg/h: n=219 Oxycodone 40 mg/d: n=220	**BTDS 20 versus BTDS 5** Treatment difference: -0.50; 95% CI: -0.90 to -0.13; p=0.006 **Favors BTDS 20** Patients receiving BTDS 20 used statistically significantly less rescue medication than patients receiving BTDS 5.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
			Oxycodone 40 mg/day versus BTDS 5 Supplemental analgesic medication: Treatment difference:-0.30; 95% CI: -0.70 to 0.09 **Not significant**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very low
Buprenorphine Versus Tramadol								
Pain relief BS-11: Change from baseline	1 RCT (Karlsson and Berggren 2009[5])	**Number of Patients:** 135 Buprenorphine: n=69 Tramadol: n=66 7-day buprenorphine patches: 5, 10, and 20 mcg/h (Maximum dose: 20 mcg/h) Tramadol PR: 70, 100, 150, and 200 mg given 2 x day (Maximum dose: 400 mg/d)	Buprenorphine: LSM: -2.26; 95% CI: -2.76 to -1.76 Tramadol: LSM: -2.09; 95% CI: -2.61 to -1.58 **Buprenorphine was non-inferior to tramadol**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Single small study)	Very low
Trials Lasting at Less Than 12 Weeks (Safety Data Only)								
Abuse-deterrent Formulations								
Constipation	1 RCT (Ahmedzai et al. 2011[6])	**Number of Patients:** 184 OXN PR: n=92 OXY PR: n=92 OXN PR: Up to 120 mg/d OXY PR: Up to 120 mg/d	Change in BFI = -11.14; 95% CI: -19.03 to -3.24; p<0.01. **Favors OXN PR**	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Single small trial)	Low
			Scores for PAC-SYM significantly improved over time for both treatment conditions (p<0.01). Degree of improvement was greater for patients receiving OXN PR relative to patients	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Very serious imprecision (-2) (Single small study; imprecise reporting of	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
			receiving OXY PR (total symptom score: p=0.014; frequency of symptoms: p<0.01) **Favors OXN PR**				statistical findings)	
Buprenorphine: Transdermal Versus Sublingual								
Adverse drug reactions	1 RCT (James et al. 2010[7])	**Number of Patients:** 238 Transdermal 5 to 20 mcg/hr: n=118 Sublingual 200 to 400 mcg/tablets: n=118	Significantly fewer patients receiving transdermal buprenorphine patches experienced adverse drug reactions relative to those receiving sublingual buprenorphine (Transdermal: 96 patients [81%]; Sublingual: 110 patients [92%]; p=0.0197) **Favors transdermal**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Very serious imprecision (-2) (Single small study; imprecise reporting of statistical findings)	Very low
Adverse	1 RCT (James et al. 2010[7])	**Number of Patients:** 238 Transdermal 5 to 20 mcg/hr: n=118 Sublingual 200 to 400 mcg/tablets: n=118	Rates of nausea (p=0.035), dizziness (p=0.026), and vomiting (p=0.039) were statistically significantly lower in patients given transdermal buprenorphine patches relative to those given sublingual buprenorphine. **Favors transdermal**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Very serious imprecision (-2) (Single small study; imprecise reporting of statistical findings)	Very low
Skin irritation	1 RCT (James et al. 2010[7])	**Number of Patients:** 238 Transdermal 5 to 20 mcg/hr: n=118 Sublingual 200 to 400 mcg/tablets: n=118	Redness was more common during the titration phase of the trial for patients receiving active transdermal buprenorphine relative to those receiving placebo patches (p=0.016) **Favors placebo patch over active patch**	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Very serious imprecision (-2) (Single small study; imprecise reporting of statistical findings)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Long-acting Versus Short-acting Formulations								
Dihydrocodeine								
Adverse	1 RCT (Pedersen et al. 2014[8]) The authors note that the study was not powered to assess adverse , and there was no statistical comparison between the groups.	**Number of Patients:** 58 LA: Dihydrocodeine: n=28 SA: Dihydrocodeine: n=30 LA: 120 to 240 mg/d given every 8 to 12 hr, SA: 120 to 240 mg/d	LA: 36 Most frequent complaints Constipation n=11 Headache n=7 Dry mouth n=4 Fatigue n=3 SA: 22 Most frequent complaints Constipation n=8 Nausea n=4 Headache n=3	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Very serious imprecision (-2) (Numerous limitations including lack of statistical analysis, single small trial, lack of statistical power)	Very low
Withdrawals from study	1 RCT (Pedersen et al. 2014[8]) The authors note that the study was not powered to assess adverse , and there was no statistical comparison between the groups.	**Number of Patients:** 58 LA: n=28 SA: n=30 LA: 120 to 240 mg/d given every 8 to 12 hr, SA: 120 to 240 mg/d	LA Adverse effects (constipation/abdominal pain): n=1 Lack of efficacy: n=4 Lack of efficacy and adverse effects (Constipation, nausea, headache, and/or lack of appetite): n=3 Lost to follow-up: n=2 SA Adverse effects (constipation): n=2 Lack of efficacy: n=4 Lack of efficacy and adverse effects (Constipation, nausea, headache, and/or lack of appetite): n=1 Lost to follow-up: n=2	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Very serious imprecision (-2) (Numerous limitations including lack of statistical analysis, single small trial, lack of statistical power)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Hydromorphone								
TEAEs	1 RCT (Yu et al. 2014[9])	**Number of Patients:** 260 ER: n=130 CR: n=130 ER hydromorphone: 8 or 16 mg given once daily CR oxycodone: 10, 20, or 40 mg given 2 x per day	Any TEAEs Hydromorphone ER: n=111 Oxycodone CR: n=117 The top ten most common TEAEs were vomiting, constipation, nausea, pyrexia, dizziness, decreased appetite, decreased white blood cell count, anemia, decreased appetite, and diarrhea.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Very serious imprecision (-2) (Numerous limitations including lack of statistical analysis, lack of precision in reporting data)	Very low

[a] Methodological Quality takes into account the overall risk of bias rating of all the studies included in the evidence base;
[b] Inconsistency of results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed);
[c] Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population; and
[d] Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.

ABC: Addiction Behaviors Checklist; scores range from 0-20 with scores ≥3 flagging for possible misuse; BFI: bowel function index; CI: confidence interval; CR: controlled-release; ER: extended release; IR: immediate release; LBPIX: low back pain intensity index; LOCF: last observation carried forward; LSM: least squares mean; MEQ: morphine equivalent; MD: mean difference; MOR: morphine; mPDI: modified Pain Disability Index; OIC: opioid-induced constipation; OR: odds ratio; OXN: oxycodone/naloxone; OXY: oxycodone; PAC-SYM: Patient Assessment of Constipation Symptoms; PR: prolonged release; QLIP: Quality of life (QOL) impairment by pain; ratings range from 40 = no impairment to 0 = maximum impairment; RR: relative risk; TEAEs: treatment-emergent adverse ; VAS: visual analog scale; ratings range from 0-10 with 0 = no pain and 10 = worst pain imaginable; WMD: weighted mean difference;

Appendix A. Evidence Tables

Table 2. Systematic Review/Meta-analysis

Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results
Morphine Versus Other Opioids			
Reference: Bekkering et al. 2011[1] **Country:** Belgium **Purpose:** Network meta-analysis to evaluate the use of morphine as the reference standard of step III opioid safety and efficacy **Quality Rating:** Fair The review authors rated studies as Fair due to limitations related to inadequate randomization, blinding, allocation concealment, and manufacturer funding source.	MEDLINE (including in-process), EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA]) 2007 onwards], Latin American and Caribbean Health Sciences (LILACS), and the GIN International Guidelines Database were searched through December 2010. The evidence base consisted of 56 randomized controlled trials (RCTs) comparing step III to placebo or to other step III opioids for treating chronic cancer or non-cancer pain. The primary outcome measures included pain intensity, pain relief, quality of life (QOL), quality of sleep, and tolerability of treatment. **Inclusion/Exclusion Criteria:** Studies needed to be RCTs or systematic reviews of RCTs in patients over the age of 18 with chronic pain with a minimum treatment of 24 hours.	**Number of Patients:** Enrollment ranged from 21 patients to 684 patients per trial. Total n not reported. **Diagnosis:** Chronic cancer or non-cancer pain. **Age:** The majority of trials enrolled a range from early 20s to 90 **Gender:** % Female ranged from 27.5% to 74% **Intervention/Comparators:** Morphine vs. comparator (16 studies, comparators below): Dose ranges for morphine: Cancer pain: 45 to 540 mg/d; non-cancer pain: 30 to 140 mg/d Placebo: 3 studies; follow-up range 7–30 days to 3–5 months Transdermal buprenorphine: 1 study 35–52.5 mcg/h; follow-up 1–2 months Transdermal fentanyl: 5 studies; 25–100 mcg/h; follow-up range 7–30 days to 12–24 months Hydromorphone: 1 study; 12–108 mg/d; follow-up 3–5 months Methadone: 4 studies; 17.7–25.2 mg/d; follow-up 7 days to 2 months Oxycodone: 4 studies; 20–101 mg/d; follow-up range 7–30 days to 6–11 months	**Pain Intensity: Comparison with Morphine** WMD >0 indicates that morphine is more effective than the comparator. Placebo 3–5 months; non-cancer pain Compared to morphine + naltrexone: morphine dose = 40 to 160 mg/d WMD=11.1; 95% CI: 5.4 to 16.8; 1 study; n=344 **Favors morphine** Fentanyl 12–24 months; 57 mcg/hr; non-cancer pain Morphine dose = 140 mg/d WMD=1.0; 95% CI: -32.6 to 34.6; 1 study; n=680 **Difference not significant** Hydromorphone 2–5 months; 12–108 mg/d; cancer pain Morphine dose = 60 to 540 mg/d WMD=6.7; 95% CI: -0.1 to 13.5; 1 study; n=200 **Difference not significant** Oxycodone 2–11 months; 34–84.7 mg/d; non-cancer pain Morphine dose = 30 to 78.7 mg/d WMD=3.9; 95% CI: -1.4 to 9.2; 2 studies; n=489 **Difference not significant** **Serious Adverse Events** Morphine vs. Other Step III Opioids RR=1.15; 95% CI: 0.79 to 1.67. Not significant. There was no difference between treatment conditions on rates of serious adverse events; 3 studies. **Treatment Discontinuation** **Cancer pain** 10 studies; n=1,047 Lack of efficacy (All comparisons not significant) **Placebo** OR=1.88; 95% CI: 0.43 to 8.20

Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results
		Higher doses were used in patients with cancer pain; lower doses were used in patients with non-cancer pain	**Buprenorphine** OR=0.48; 95% CI: 0.07 to 3.14 **Fentanyl** OR=1.20; 95% CI: 0.39 to 3.65 **Hydromorphone** OR=3.03; 95% CI: 0.93 to 9.87 **Methadone** OR=0.89; 95% CI: 0.31 to 2.54 **Oxycodone** OR=1.09; 95% CI: 0.07 to 17.8 Adverse Events **Placebo** OR=6.27; 95% CI: 0.74 to 53.12 **Not significant.** **Fentanyl** OR=0.12; 95% CI: 0.04 to 0.36; **Favors fentanyl**. Patients receiving fentanyl were less likely to drop out due to adverse events than patients receiving morphine. **Hydromorphone** OR=1.46; 95% CI: 0.64 to 3.36 Not significant **Methadone** OR=3.00; 95% CI: 1.11 to 8.11 **Favors morphine**. Patients receiving methadone were more likely to drop out due to adverse events than patients receiving morphine. **Oxycodone** OR=0.51; 95% CI: 0.12 to 2.17 Not significant **Non-cancer pain** 27 studies; n=8,177 Lack of efficacy **Placebo** OR=3.71; 95% CI: 2.27 to 6.08 **Favors morphine** Patients receiving placebo were more likely to drop out due to lack of efficacy than patients receiving morphine. **Buprenorphine** OR=2.37; 95% CI: 1.32 to 4.28 **Favors morphine** Patients receiving buprenorphine were more likely to drop out due to lack of efficacy than patients receiving morphine. **Fentanyl** OR=0.82 ; 95% CI: 0.48 to 1.40 Not significant **Hydromorphone** OR=0.94; 95% CI: 0.51 to 1.74 Not significant **Oxycodone** OR=0.71; 95% CI: 0.43 to 1.16 Not significant **Oxymorphone** OR=0.73; 95% CI: 0.39 to 1.39 Not significant

Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results
			Adverse Events **Placebo** OR=0.13; 95% CI: 0.08 to 0.21 **Favors placebo** Patients receiving placebo were less likely to drop out due to adverse events than patients receiving morphine **Buprenorphine** OR=0.49; 95% CI: 0.24 to 0.99 **Favors buprenorphine** Patients receiving buprenorphine were less likely to drop out due to adverse events than patients receiving morphine **Fentanyl** OR=0.41; 95% CI: 0.19 to 0.87 **Favors fentanyl** Patients receiving fentanyl were less likely to drop out due to adverse events than patients receiving morphine **Hydromorphone** OR=0.77; 95% CI: 0.44 to 1.35 Not significant **Oxycodone** OR=0.92; 95% CI: 0.58 to 1.49 Not significant **Oxymorphone** OR=0.78; 95% CI: 0.40 to 1.51 Not significant Data for QoL, quality of sleep, and pain relief were reported in Supplemental Tables referred to in the article but these tables were no longer available on the publisher's website.
Tapentadol			
Reference: Santos et al. 2015[2] **Country:** Portugal **Purpose:** To determine the efficacy, safety, and tolerability of tapentadol extended-release (ER) for moderate-to-severe pain for at least three months for any musculoskeletal cause **Quality Rating:** Fair The review authors rated 2 studies as having high risk of bias due to incomplete outcome data; and rated 2	CENTRAL, MEDLINE, EMBASE, and the Web of Science were searched to March 2014 Trials registers and reference lists from retrieved studies were also searched The evidence base consisted of 4 RCTs comparing tapentadol extended-release to oxycodone controlled release or to placebo (placebo data considered in chapter for KQ3/4) **Inclusion/Exclusion Criteria:** RCTs (published and unpublished, where randomization was explicit and appropriate) comparing tapentadol with placebo, other strong analgesic agents, both or other active controls; adults aged	**Number of Patients:** 4,094 **Diagnosis:** Chronic osteoarthritis or back pain **Age:** Generally not reported, ~40 years when reported **Gender:** % Female not reported **Intervention/Comparators:** Tapentadol expended release (100 to 250 mg/day) Oxycodone controlled release (20 to 50 mg/day)	**Change in Pain Intensity from Baseline:** MD= -0.24 95% CI: -0.43 to -0.05. **Favors tapentadol**. Patients taking tapentadol had greater reductions in pain intensity from baseline relative to patients taking oxycodone. (4 studies; total n=3,116) **Efficacy in Responders (those at least 50% pain reduction):** RR=1.46; 95% CI: 0.92, 2.32. **Not significant**. (2 studies; n=1,327) **Serious Adverse Events:** RR=0.57; 95% CI: 0.24 to 1.33. **Not significant**. (4 studies; n=3,099) **Adverse Effects:** RR=0.91; 95% CI: 0.85 to 0.96. **Favors tapentadol**. (3 studies; n=2,449) **Discontinuation Due to Adverse Effects: RR=0.50; 95% CI: 0.42 to 0.60. Favors tapentadol** (4 studies; n=3,102)

Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results
study as having a high risk of due to concerns regarding the outcomes selected and lacking an allocation concealment description. The authors reported finding no evidence for publication bias.	18 years or older with moderate-to-severe chronic musculoskeletal pain (at least 3 months) of any cause.		Patients taking tapentadol were less likely to experience adverse effects of treatment than patients taking oxycodone.

CI: confidence interval; MD: mean difference; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; WMD: weighted mean difference

Table 7. Individual Studies

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Trials Lasting at Least 12 Weeks			
Abuse-deterrent Formulations			
Reference: Ueberall and Mueller-Schwefe 2015[3] **Country:** Germany **Study Design:** RCT; open-label; blinded endpoint **Purpose:** To determine the safety and tolerability of oxycodone/naloxone (OXN) relative to oxycodone (OXY) or morphine (MOR) **Quality Rating:** Poor High and differential attrition (28.5% to 41.1%). ITT used. Randomization adequate, but patients and physicians not blinded to treatment. Randomization pertained to assigning participants to a treatment condition. However,	**Number of Patients:** 453 OXN: n=144 OXY: n=151 MOR: n=158 **Diagnosis:** Chronic low back pain **Age (Years):** 46.3 (9.7) **Gender:** 43.7% male **Inclusion Criteria:** Over 18 years of age, non-pregnant/non-lactating, history of moderate to severe non-malignant chronic low back pain, previously treated with WHO Step I or Step II analgesics with unsuccessful pain management or unacceptable side effects and requiring around-the-clock therapy. **Exclusion Criteria:** Contraindications for use of any of the study medications, including respiratory depression, COPD, pulmonary hypertension, severe asthma, paralytic ileus, moderate to severe liver or kidney impairment;	**Treatment**: For opioid naïve patients, the recommended starting dose was 20 mg morphine equivalent (MEQ)[1] for prolonged release treatments. Dose adjustments were made at the discretion of the physician. Medications were prescribed by participating physicians and were not provided by the investigators. Initial starting dose: Mean (SD) MEQ OXN: 29.3 (10.2) mg OXY: 28.9 (10.3) mg MOR: 29.8 (11.7) mg Study completion dose: Mean (SD) MEQ OXN: 124.1 (25.3) mg OXY: 120.0 (29.7) mg MOR: 126.7 (26.1) mg **Rescue Medication:** Use was permitted at the physician's discretion	**Pain relief** **mPDI ≥50% improvement from baseline** OXY vs. OXN: OR=1.64; 95% CI: 1.03 to 2.60; p<0.001; **Favors OXN** MOR vs. OXN: OR=1.83; 95% CI: 1.16 to 2.89; p<0.001; **Favors OXN** MOR vs. OXY: OR=1.12; 95% CI: 0.72 to 1.75; p=0.36. Not significant. **LBPIX ≥50% improvement from baseline** OXY vs. OXN: OR=2.09; 95% CI: 1.27 to 3.44; p<0.001; **Favors OXN** MOR vs. OXN: OR=2.71; 95% CI: 1.66 to 4.42; p<0.001; **Favors OXN** MOR vs. OXY: OR=1.30; 95% CI: 0.83 to 2.04; p=0.19. Not significant. **QoL ≥50% improvement from baseline** OXY vs. OXN: OR=2.07; 95% CI: 1.30 to 3.31; p<0.001; **Favors OXN**

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
treatments were prescribed at the discretion of the patient's physician.	planned surgery that would influence pain or bowel function; participation in the previous 30 days in any research study involving experimental medications; and irritable bowel syndrome or other gastrointestinal disease.	**Outcomes (Instrument)**: Pain (mPDI; German Pain Diary; Low back pain intensity index [LBPIX]); Quality of life (QLIP Inventory); TEAEs; OIC (BFI) Data are reported as combined Primary and Secondary endpoints.[2] Where possible, data for individual outcomes are presented here. **Follow-up:** 12 weeks	MOR vs. OXN: OR=2.50; 95% CI: 1.57 to 3.99; p<0.001; **Favors OXN** MOR vs. OXY: OR=1.21; 95% CI: 0.77 to 1.89; p=0.15. Not significant. **BFI Increase ≤50% from baseline** OXY vs. OXN: OR=2.41; 95% CI: 1.45 to 3.99; p<0.001; **Favors OXN** MOR vs. OXN: OR=2.75; 95% CI: 1.67 to 4.52; p<0.001; **Favors OXN** MOR vs. OXY: OR=1.14; 95% CI: 0.73 to 1.79; p=0.30. Not significant **Adverse Events** Statistically significantly fewer patients taking OXN (14.6%) reported experiencing at least one TEAE than patients taking OXY (29.1%); The difference was not quite significant between OXN and MOR (23.4%). OXN vs. OXY: OR=2.41; 95% CI: 1.35 to 4.31. **Favors OXN** OXN vs. MOR: OR=1.79; 95% CI: 0.99 to 3.24. **Not significant** There were no serious adverse events reported. The most commonly reported TEAEs were: Constipation, nausea, somnolence, dizziness, and sleep problems. **TEAE-related treatment discontinuations** OXY vs. OXN: OR=2.28; 95% CI: 1.20 to 4.32; p<0.001; **Favors OXN** MOR vs. OXN: OR=2.79; 95% CI: 1.48 to 5.26; p<0.001; **Favors OXN** MOR vs. OXY: OR=1.22; 95% CI: 0.73 to 2.07; p=0.22. Not significant.
Buprenorphine (Transdermal)			
Reference: Steiner et al. 2011[4] **Country:** USA **Study Design:** RCT **Purpose:** To determine the efficacy and safety of	**Number of Patients:** 662 randomized into the trial BTDS 5: n=221 BTDS 20: n=219 Oxycodone: n=220	**Treatment**: BTDS 5: 5 mcg/h buprenorphine; patch lasts 7 days BTDS 20: 20 mcg/h buprenorphine; patch lasts 7 days	**Average Pain Over the Previous 24 hours** **BTDS 5 vs. BTDS 20*** Difference from BTDS 5 over weeks 4,8, and 12: -0.67 95% CI: -0.99 to -0.35

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
buprenorphine transdermal system (BTDS) relative to active control (immediate release oxycodone 40-mg/day) **Quality Rating:** Poor Trial halted early, <80% follow-up; ITT used. Randomization adequate. Medications administered according to double-blind, double-dummy procedure.	**Diagnosis:** Chronic, moderate to severe low back pain **Age (SD):** 50 (12.39) **Gender:** 52% male **Inclusion Criteria:** Over 18 years of age with history of moderate to severe non-malignant chronic low back pain requiring 30 to 80 mg/d of oral morphine sulfate or MEQ/d at least 4 x a week, for at least the 30 days before the screening visit. **Exclusion Criteria:** Patients could not have been receiving frequent analgesic therapy for other chronic conditions such as gout, fibromyalgia, headaches.	Oxycodone: 2 5–mg immediate-release oxycodone capsules given every 6h total dose 40 mg/day All trial medications given according to double-blind, double-dummy scheme **Rescue Medication:** Use was permitted; but use within 24-h prior to pain assessments rendered that day's pain score as invalid. Data for that day were interpolated using 2 adjacent valid pain scores **Outcomes (Instrument)**: "Average pain over the last 24 hours" score obtained during study visits; Oswestry Disability Index (ODI); Sleep Disturbance as measured by the Medical Outcome Study (MOS)-Sleep **Follow-up:** 12 weeks **Trial note:** "The primary treatment comparison was between the BTDS 20 and BTDS 5 treatment groups and only used data observed while patients were exposed to study drug. Comparison between the BTDS 5 and the oxycodone 40 mg/day treatment groups was conducted to evaluate the assay sensitivity of the study. The study was not sized to detect differences between BTDS 20 and oxycodone 40 mg/day."	Pain was statistically significantly lower for patients receiving BTDS 20 relative to patients receiving BTDS 5. **Favors BTDS 20** **BTDS 5 vs. Oxycodone** Difference from BTDS 5 over weeks 4,8, and 12: -0.075; 95% CI: -1.07 to -0.44 Pain was statistically significantly lower for patients receiving oxycodone relative to patients receiving BTDS 5. **Favors Oxycodone** **BTDS 20 versus BTDS 5** MOS sleep disturbance subscale: Treatment difference: -6.23; 95% CI: -9.64 to -2.82; p<0.001 **Favors BTDS 20** Patients receiving BTDS 20 had statistically significantly lower sleep disturbance than patients receiving BTDS 5. ODI score: Treatment difference: -1.72; 95% CI: -3.55 to 0.11 **Not significant** Supplemental analgesic medication: Treatment difference: -0.50; 95% CI: -0.90 to -0.13; p=0.006 **Favors BTDS 20** Patients receiving BTDS 20 used statistically significantly less rescue medication than patients receiving BTDS 5. **Oxycodone 40 mg/day versus BTDS 5** MOS sleep disturbance subscale: Treatment difference: -2.65; 95% CI: -6.01 to 0.70 **Not significant** ODI score: Treatment difference: -1.99; 95% CI: -3.79 to -0.18 **Not significant **** Supplemental analgesic medication: Treatment difference: -0.30; 95% CI: -0.70 to 0.09 **Not significant** **Adverse events related to substance misuse (Narrative description)** "Three SAEs were related to drug abuse. Cocaine abuse was recorded as an SAE for the patient who died during the run-in period.

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			Oxycodone abuse during the double-blind phase was recorded as an SAE for a second patient who completed the study. Hydrocodone/acetaminophen abuse during the double-blind phase was recorded as an SAE for a third patient whose abuse of this non-protocol specified medication had been discovered after the patient had completed the study. Additionally, a patient who was receiving BTDS 5 in the double-blind phase discontinued from the study due to an SAE that was associated with suspected BTDS abuse." ***Statistical measure =** repeated measures, mixed effects linear model with treatment and time as fixed effects, screening mean pain and pre-randomization mean pain as covariates, and patient as a random effect. ** Not significant according to stepwise gate-keeping analysis α-level .05/3.
Reference: Karlsson and Berggren 2009[5] **Country:** Sweden **Study Design:** Open-label, non-inferiority RCT **Purpose:** To determine the safety and efficacy of low-dose transdermal buprenorphine relative to tramadol PR in patients with chronic osteoarthritis pain. **Quality Rating: Poor** Less than 80% follow-up; ITT used. Randomization adequate. Open label trial—perception of pain is known to be subject to expectation effects. Lack of reporting on data for pre-specified outcomes.	**Number of Patients:** 135 Buprenorphine: n=69 Tramadol: n=66 **Diagnosis:** Chronic osteoarthritis (OA) pain **Age (Years):** 64.3 **Gender:** 29 % male **Inclusion Criteria:** Over 18 years of age with a clinical diagnosis of OA of the hip and/or knee, based on American College of Rheumatology and radiographic criteria. Patients needed to experience inadequate pain relief while taking immediate-release paracetamol 4000 mg/d during the screening week **Exclusion Criteria:** Patients were excluded if they were treated for OA pain with high-potency opioid analgesics for >1 week in the past 3 months; or if they required frequent analgesic therapy for other chronic conditions; were abusing controlled substances or alcohol or, "in the opinion of the investigator, demonstrated	**Treatment**: 7-day buprenorphine patches: 5, 10, and 20 mcg/h (Maximum dose: 20 mcg/h) Tramadol PR: 70, 100, 150, and 200 mg given 2 x day (Maximum dose: 400 mg/d) **Rescue Medication:** Use of paracetamol was permitted throughout the trial **Outcomes (Instrument)**: Pain scores (Box Scale 11 [BS-11]); Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index; EuroQol EQ-5D health states index; EuroQol visual analog scale (EQ-VAS). **Follow-up:** 12 weeks	**BS-11: Change from baseline** Buprenorphine: LSM: -2.26; 95% CI: -2.76 to -1.76 Tramadol: LSM: -2.09; 95% CI: -2.61 to -1.58 **Buprenorphine was non-inferior to tramadol** **Adverse Events:** Rates of adverse events were reported to be similar between the two treatment conditions, but the authors state "There were too few events in the various Medical Dictionary for Regulatory Activities organ classes to draw any conclusions regarding differences between the treatments." The most common adverse events were nausea, constipation, dizziness, fatigue, and pain

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	behaviors suggestive of addiction or substance abuse;" cancer (except basal cell carcinoma) within the previous 5 years.		Scores on the WOMAC, EuroQol EQ-5D and EQ-VAS were described as being similar between groups but no data were reported.
Trials Lasting at Less Than 12 Weeks (Safety Data Only)			
Abuse-deterrent Formulations			
Reference: Ahmedzai et al. 2011[6] **Country:** Germany **Study Design:** RCT; 4-week trial* **Purpose:** To determine the safety and efficacy of oxycodone/naloxone prolonged-release (OXN PR) relative to oxycodone prolonged-release (OXY PR) in patients with moderate to severe chronic cancer pain. **Quality Rating: Fair** Modest attrition; ITT used. Lack of precision in reporting test statistics. Lack of clarity in reporting outcomes. *Per protocol, outcomes of interest for short term trials (<12 weeks) relate to safety only.	**Number of Patients:** 184 OXN PR: n=92 OXY PR: n=92 **Diagnosis:** Chronic cancer pain **Median Age (Years):** 64 **Gender:** 51.1% male **Inclusion Criteria:** Over 18 years of age with moderate to severe chronic cancer pain and requiring around-the-clock therapy equivalent to OXY PR 20–80 mg/d at the start of the trial. **Exclusion Criteria:** Clinically unstable disease, significant cardiovascular, renal, hepatic, GI, or psychiatric disease, cyclic chemotherapy within 2 weeks of screening or during the study, or radiotherapy.	**Treatment**: OXN PR: Up to 120 mg/d OXY PR: Up to 120 mg/d **Rescue Medication:** Oxycodone immediate-release was available as rescue medication, with a maximum of six doses per 24 h **Outcomes (Instrument)**: Safety and adverse events (BFI, Patient Assessment of Constipation Symptoms [PAC-SYM]) **Follow-up:** 4 weeks	**Constipation** **BFI (Change from baseline; LOCF analysis)**: Change in BFI = -11.14; 95% CI: -19.03 to -3.24; p<0.01. **Favors OXN PR** **PAC-SYM**: Scores for PAC-SYM significantly improved over time for both treatment conditions (p<0.01). Degree of improvement was greater for patients receiving OXN PR relative to patients receiving OXY PR (total symptom score: p=0.014; frequency of symptoms: p<0.01) **Favors OXN PR** **Adverse Events:** Approximately 20% of AEs reported in this trial were related to cancer progression. 18 patients (10%) died during the 4 week trial: progression of malignant disease n=16; cardiac disorders: n=2. Rates of adverse events did not vary statistically between the two treatment conditions. The most commonly reported advents were related to GI function (e.g., nausea, vomiting, abdominal pain) and "general disorders and administration site conditions." Note: there is lack of clarity regarding the definition of "administration site conditions." Medications were provided in tablets and taken *per os*.
Buprenorphine: Transdermal Versus Sublingual			
Reference: James et al. 2010[7] **Country:** United Kingdom **Study Design:** Double-Blind, Double-Dummy RCT*	**Number of Patients:** 238 Transdermal: n=118, Completed: n=56 Sublingual: n=118, Completed: n=54 **Diagnosis:** Chronic osteoarthritis pain	**Treatment**: Transdermal: 5 to 20 mcg/hr Sublingual: 200 to 400 mcg/tablets	**Adverse Events** Significantly fewer patients receiving transdermal buprenorphine patches experienced adverse drug reactions relative to those receiving sublingual buprenorphine

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Purpose: To compare the efficacy and tolerability of low-dose transdermal buprenorphine to buprenorphine sublingual tablets in patients with chronic osteoarthritis pain **Quality Rating: Poor** High attrition <60% follow-up); ITT used. Randomization and blinding adequate. Lack of precision in reporting test statistics (only reported p values). *Per protocol, outcomes of interest for short term trials (<12 weeks) relate to safety only.	**Mean Age (Years):** 64.3 **Gender:** 43.5% male **Inclusion Criteria:** 18–80 years of age with moderate to severe osteoarthritis pain. **Exclusion Criteria:** Use of Step III opioids within the previous 6 weeks, long-acting NSAIDS within the previous 7 days, or modified-release NSAIDS within the previous 24 hours of enrollment; intra-articular injection in the previous six weeks or having one scheduled within the study period; or having any other chronic pain condition than osteoarthritis.	**Rescue Medication:** Oral paracetamol (500 mg) was permitted up to a maximum daily dose of 4,000 mg/d **Outcomes (Instrument)**: Safety and adverse **Follow-up:** Up to 7 weeks	(Transdermal: 96 patients [81%]; Sublingual: 110 patients [92%]; p=0.0197) The most commonly reported adverse effects were: nausea, dizziness, vomiting, somnolence, headache, and asthenia. Rates of nausea (p=0.035), dizziness (p=0.026), and vomiting (p=0.039) were statistically significantly lower in patients given transdermal buprenorphine patches relative to those given sublingual buprenorphine. Skin irritation as indicated by irritation and swelling did not vary statistically between the two treatment conditions. Patients reported that skin reactions were mild to moderate. Redness was more common during the titration phase of the trial for patients receiving active transdermal buprenorphine relative to those receiving placebo patches (p=0.016)
Long-acting Versus Short-acting Formulations			
Dihydrocodeine			
Reference: Pedersen et al. 2014[8] **Country:** Norway **Study Design:** Double-blind, double-dummy RCT; 8-week trial* **Purpose:** To determine the safety and efficacy of long-acting (LA) dihydrocodeine relative to short-acting (SA) dihydrocodeine in patients with chronic non-malignant pain. **Quality Rating: Poor** Modest attrition; ITT used for efficacy, but trial was not powered to assess adverse events. Adequate	**Number of Patients:** 58 LA dihydrocodeine: n=28 SA dihydrocodeine: n=30 **Diagnosis:** Chronic pain (Most common diagnosis: Low back pain) **Age:** LA dihydrocodeine: 49 years SA dihydrocodeine: 44.5 years **Gender:** LA dihydrocodeine: 39% male SA dihydrocodeine: 53% male **Inclusion Criteria:** 18 to 75 years of age with chronic non-malignant pain and previous maintenance on codeine (155 to 300 mg/d) at the start of the trial. All patients took codeine in combination with paracetamol prior to the trial.	**Treatment**: Dose of dihydrocodeine was given in comparable dose levels as pre-study codeine intake All patients received paracetamol in addition to dihydrocodeine. Paracetamol dose was given based on pre-study intake (Range: 2 to 4 g/d) LA dihydrocodeine: 120 to 240 mg/d given every 8 to 12 hr, with placebo (for SA) and paracetamol given 4 x per day. SA dihydrocodeine: 120 to 240 mg/d and paracetamol given 4 x per day, with placebo (for LA) taken 2 x per day. **Rescue Medication:** Rescue medication was not permitted during the trial. **Outcomes**: Adverse **Follow-up:** 8 weeks	The authors note that the study was not powered to assess adverse events, and there was no statistical comparison between the groups. **Adverse Events:** LA: 36 Most frequent complaints: Constipation n=11 Headache n=7 Dry mouth n=4 Fatigue n=3 SA: 22 Most frequent complaints Constipation n=8 Nausea n=4 Headache n=3

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
randomization. Lack of precision in reporting adverse event data. Distribution of male and female patients not equal. There was a change in medication formulation such that approximately half of the patients received medication that was visually different from the other half, medications were delivered in sealed packaging to preserve double-blinding, *Per protocol, outcomes of interest for short term trials (<12 weeks) relate to safety only.	**Exclusion Criteria:** Severe mental disorders, known substance use disorder, liver failure, or active cancer.		**Withdrawals from Study** LA: Adverse effects (constipation/abdominal pain): n=1 Lack of efficacy: n=4 Lack of efficacy and adverse effects (Constipation, nausea, headache, and/or lack of appetite): n=3 Lost to follow-up: n=2 SA Adverse effects (constipation): n=2 Lack of efficacy: n=4 Lack of efficacy and adverse effects (Constipation, nausea, headache, and/or lack of appetite): n=1 Lost to follow-up: n=2
Hydromorphone			
Reference: Yu et al. 2014[9] **Country:** China **Study Design:** Double-blind, double-dummy, RCT; 4-week trial* **Purpose:** To determine the safety and efficacy of hydromorphone extended release (ER) relative to twice-daily controlled-release oxycodone (CR) in patients with chronic cancer pain. **Quality Rating: Poor** High attrition; ITT used. Randomization adequate. Lack of precision in reporting adverse event and mortality data. *Per protocol, outcomes of interest for short term trials (<12 weeks) relate to safety only.	**Number of Patients:** 260; Completed 28-day maintenance: n=137 ER: n=130; Included in adverse event data: n=128; Completed maintenance: n=70 CR: n=130; Included in adverse event data: n=126; Completed maintenance: n=67 **Diagnosis:** Chronic cancer pain **Age:** 53.1 years **Gender:** 65.3% male **Inclusion Criteria:** 18 to 70 years of age with chronic cancer pain and eligible to move to Step 3 opioids. All patients took between 40 and 184 mg of morphine or MEQs prior to the trial. **Exclusion Criteria:** Life expectancy <12 weeks; pure neuropathic pain, acute pain, or pain of unknown origin; pregnancy or lactation; central nervous system disorder; or having "risks of treatment with study medication...outweigh the potential benefits."	**Treatment**: ER hydromorphone: 8 or 16 mg given once daily, with placebo (for CR and ER) given 2 x per day. CR oxycodone: 10, 20, or 40 mg given 2 x per day, with placebo (for ER) taken 2 x per day. **Rescue Medication**: Use of morphine immediate release (IR) was permitted as a rescue medication (5 or 10 mg). Adjuvant medications were permitted if the patients were on a stable dose that needed to be maintained. **Outcomes**: TEAEs **Follow-up:** 4 weeks	**TEAEs:** Any TEAEs Hydromorphone ER: n=111 Oxycodone CR: n=117 The top ten most common TEAEs were vomiting, constipation, nausea, pyrexia, dizziness, decreased appetite, decreased white blood cell count, anemia, decreased appetite, and diarrhea. **Study Discontinuation and Withdrawals:** During the 2 to 8-day titration period 23 patients in the ER group and 19 patients in the CR did not continue to the 28-day maintenance phase. Reasons included: Safety reasons, requiring more than the maximum dosage permitted for the trial, withdrawn consent, loss to follow-up, and "other." During the 28-day maintenance phase, 37 patients in the ER group and 44 patients in the CR did not complete the trial. 4 patients in each treatment condition died due to

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			causes unrelated to treatment. Other reasons included: Safety reasons, requiring more than the maximum dosage permitted for the trial, withdrawn consent, loss to follow-up, and "other." **Mortality:** 24 deaths were reported Hydromorphone ER: n=8 (6.3%) Oxycodone CR: n=16 (12.7%) No deaths were related to treatment condition. The most common reason for death was disease progression (number not reported).

[1] Where morphine equivalent doses are presented, they are as described within each manuscript.

[2] **Primary endpoint** was defined as patients who presented at study end with a combination of (a) lack of a premature treatment discontinuation, (b) a BFI worsening of ≤50% (vs. baseline) and (c) a ≥50% improvement (vs. baseline) with respect to any of the following three parameters: LBPIX, pain-related disabilities in daily life (assessed with the modified pain disability index, mPDI) and QoL; assessed with the QLIP inventory); **Secondary endpoint** was defined as meeting criteria (a) and (b) for the primary endpoint; however, (c) could be reflected as showing a ≥50% improvement in only one of the three efficacy parameters.

BFI: bowel function index; BTDS: buprenorphine transdermal delivery system; COPD: chronic obstructive pulmonary disease; CR: controlled release; ER: extended release; ITT: intention to treat; LA: long-acting; LBPIX: low back pain intensity index; LOCF: last observation carried forward; LSM: least squares mean; mPDI: modified Pain Disability Index; MOR: morphine; MOS: medical outcome study; ODI: Oswestry Disability Index; OIC: opioid-induced constipation; OXN: oxycodone/naloxone; OXY: oxycodone; PR: pain relief; QLIP: Quality of life (QOL) impairment by pain; ratings range from 40 = no impairment to 0 = maximum impairment; RCT: randomized controlled trial; SA: short-acting; SAE: serious adverse event; SD: standard deviation; TEAE: treatment-emergent adverse event; VAS: visual analog scale; ratings range from 0-10 with 0 = no pain and 10 = worst pain imaginable;

Appendix B. References

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Appendix C. Excluded Studies

Table 4. Excluded Studies

Reference	Reason for Exclusion
Hamza et al. 2015[10]	Does not address key question
Kleeberg et al. 2015[11]	Condition is not chronic pain (e.g., post-operative pain, palliative care)
Leng et al. 2015[12]	Pain defined as at least 4 weeks, data for true chronic pain patients not extractable
Thakur et al. 2015[13]	All included papers either do not meet inclusion criteria or are included for KQ3/4, or included in Santos 2015.[2] One individual paper included for KQ5.[6]
Ueberall and Mueller Schwefe 2015[14]	Post-hoc analysis
Burness et al. 2014[15]	Not a systematic review or clinical trial of any design (e.g., Narrative review, opinion paper, previous guideline)
Coluzzi and Ruggeri 2014[16]	3 primary studies included in Santos 1015[2] review, 2 primary studies published prior to 2009, one study is a pooled analysis of 2 studies including 1 published prior to 2009
Etropolski et al. 2014[17]	Pooled analysis
Imanaka et al. 2014[18]	Condition is not chronic pain (e.g., post-operative pain, palliative care)
Lux et al. 2014[19]	Crossover trial does not report outcomes for each phase of study
Nalamachu et al. 2014[20]	Does not meet study design criteria
Passik et al. 2014[21]	Post-hoc analysis of excluded study by Webster et al. 2013[22]
Zeppetella G, Davies A, Eijgelshoven I, Jansen JP 2014[23]	Short-term interventions do not report on safety outcomes
Zimmermann and Richarz 2014[24]	No extractable data
Merchant et al. 2013[25]	Post-hoc analysis of papers[26,27] that are included in Santos 2015[2]
Richarz et al. 2013[28]	Long term data from Binsfield[29]. Included in Bekkering[1]
Webster et al. 2013[22]	Crossover trial does not report outcomes for each phase of study. Unable to determine what treatments are being used in the open-label phase
De La Iglesia et al. 2012[30]	7 day crossover trial, report of two previously conducted trials
Ling et al. 2012[31]	Fewer than 20 patients enrolled
Nampiaparampil et al. 2012[32]	Opioid-focused studies published prior to 2009
Ridgway et al. 2012[33]	Population not of interest
Taylor et al. 2012[34]	Qualifying studies included in Santos 2015[2]
Wolff et al. 2012[35]	All studies published prior to 2009
Wolff et al. 2012[36]	Does not meet study design criteria
Kocher and Kadaba 2011[37]	One relevant paper, published in 1999
Mejjadet al. 2011[38]	Does not meet study design criteria
Naliboff et al. 2011[39]	Unable to determine what treatments are being used in the trial, dose escalation is primary intervention, but dose of treatment medication increased for both groups over the study, possibly confounding observed results

Reference	Reason for Exclusion
Binsfeld et al. 2010[29]	Included in Bekkering[1]
Dasgupta et al. 2010[40]	No info on acute vs. chronic pain among patient population
Etropolski et al. 2010[41]	Crossover trial does not report outcomes for each phase of study; no washout period cannot preclude possibility of carryover effects
Lange et al. 2010[42]	Pooled analysis of data from two conference presentations from 2009
Mercadante et al. 2010[43]	Included in Bekkering[1]
Wild et al. 2010[44]	Included in SR by Santos 2015[2]
Argoff et al. 2009[45]	Not a systematic review or clinical trial of any design (e.g., Narrative review, opinion paper, previous guideline)
Devulder et al. 2009[46]	Searches ended in 2006
Guay 2009[47]	Not a systematic review or clinical trial of any design (e.g., Narrative review, opinion paper, previous guideline)
Hartrick et al. 2009[48]	Included in Bekkering[1]
Löwenstein et al. 2009[49]	Population not of interest
Meissner et al. 2009[50]	Upon reviewing full text: Does not address a key question
Tassinari et al. 2009[51]	All trials 2005 or older

Key Question 6: Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to opioid therapy alone?

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Key Question 6: Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to opioid therapy alone?

Summary of Evidence Base

The searches identified four studies; a post-hoc analysis (Peniston et al. 2012[1]), a retrospective cohort study (Turner and Liang 2015[2]), a randomized controlled trial (RCT) (Baron et al. 2015[3]), and a prospective comparison study (Mustafa et al. 2010[4]) as evidence for this key question. Two studies addressed the additional use of antidepressants (ADs)[2,4] while one study each evaluated the addition of benzodiazepines,[2] pregabalin,[3] selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs),[1] and zolpidem.[2]

- Adding ADs: One retrospective cohort study[2] determined long-term AD usage (91–180 days) was protective in patients with depression with 20% lower adjusted odds ratios (AORs) for overdose versus short-term (1–30 days) or none. For individuals without depression, the AORs of overdose were increased for AD use, but greatest (AOR 1.98, 95% CI: 1.48 to 2.65) for short-term use versus none (Strength of evidence (SOE): moderate). One prospective comparison trial[4] indicated slightly fewer patients receiving combination oral morphine sulfate (MST)/AD therapy reported tolerable side effects than patients receiving MST monotherapy at 8 weeks (29.6% MST, 27.5% MST/AD) Combination therapy however lessened the total frequency of side effects of both MST and AD (MST: 12.4% combination therapy, 21.2% MST monotherapy; AD: 18.6% combination therapy, 37.6% AD monotherapy)(SOE: very low).
- Adding benzodiazepines: One retrospective cohort study[2] noted that AORs of overdose increased with duration of benzodiazepine with >2.5-fold higher AORs for 91–180 days (with or without posttraumatic stress disorder (PTSD)/anxiety) vs. none for all patients (SOE: moderate).
- Adding pregabalin: One RCT[3] reported mixed results for tolerability for tapentadol prolonged release (PR)/pregabalin combination therapy (300 mg/day each) versus tapentadol PR monotherapy (500 mg/day). Outcomes included a similar percent of patients reporting ≥1 treatment-emergent adverse events (TEAEs), a lower incidence of serious TEAEs with pregabalin, and a higher incidence of composite outcome of dizziness/somnolence with pregabalin (SOE: moderate).
- Adding SSRIs or SNRIs: One post-hoc analysis[1] indicated significantly more serious AEs occurred in patients taking SSRIs/SNRIs plus oxymorphone extended release (ER) versus oxymorphone ER monotherapy during the open-label phase (3.4% oxymorphone ER plus SSRIs/SNRIs, 0.8% oxymorphone ER; p=0.04) but no differences were reported for serious AEs during the double-blind phase or overall frequency of AEs (SOE: very low).
- Adding zolpidem: One retrospective cohort study[2] determined for patients with anxiety/PTSD, the AORs of overdose were greatest for 31–90 days vs. none (AOR 1.77, 95% CI: 1.25 to 2.51). For patients without anxiety/PTSD, the AORs of overdose were greatest for short-term use versus none (AOR 1.67 (95 % CI: 1.21 to 2.30) (SOE: moderate).

Overview of Evidence Base

Our searches of the literature identified four studies; 1 post-hoc pooled analysis,[1] 1 retrospective cohort study,[2] 1 RCT,[3] and 1 prospective comparison trial[4] that considered the evidence for adding benzodiazepines or other psychoactive medications to opioids in treating patients with chronic pain. Peniston et al. 2012[1] was a post-hoc pooled analysis of two RCTs assessing the tolerability of adding SSRIs or SNRIs to oxymorphone ER for treating moderate-to-severe CLBP patients. The second study (Turner and Liang 2015[2]) was a retrospective cohort examining interactions of filled prescriptions for opioids, benzodiazepines, antidepressants, and zolpidem with drug overdose and mental health disorders such as anxiety/PTSD and depression.[2] The third study (Baron et al. 2015 RCT[3]) evaluated the tolerability of tapentadol PR monotherapy versus tapentadol PR/pregabalin combination therapy for patients with severe CLBP with a neuropathic component. Lastly, a prospective comparison trial (Mustafa et al. 2010[4]) evaluated the analgesic efficacy of oral MST monotherapy versus MST/AD combination therapy for management of chronic pain patients. Studies excluded as evidence for this key question and exclusionary reasons are presented in Table 3 of the Appendix.

Study Quality Rating

One post-hoc pooled analysis (Peniston et al. 2012[1]) was rated Poor due to lack of reporting on the study quality of included studies and high drop-out rate. One retrospective cohort (Turner and Liang 2015[2]) was rated Fair due to use of multivariate analysis controlling for most confounders and low attrition. However, limitations such as use of coded diagnoses with limited sensitivity for mental health disorders and lack of determining adherence to prescriptions downgraded this rating. One double-blind RCT (Baron et al. 2015[3]) was rated Good due to well-matched baseline characteristics, >80% followup, and evaluation of efficacy outcomes using the last observation carried forward approach. One prospective comparative trial (Mustafa et al. 2010[4]) was rated Poor due to lack of randomization of patients or attention to confounders. Authors also reported limited baseline characteristics.

Overview of Study, Patient, and Intervention Characteristics

Below we provide a brief description of the study, patient, and intervention characteristics of the studies that make up the evidence base for this key question. Additional information is provided in Table 2.

Adding Antidepressants

One prospective comparative study (Mustafa et al. 2010[4]) evaluated the tolerability of oral MST monotherapy versus combined MST/AD to manage patients with chronic cancer and non-cancer pain. The study evaluated 527 patients with a mean age of 46.5 years (64.9% males). All patients were started on 4-week AD therapy. After evaluations of VAS pain scores and tolerability, patients were either maintained on ADs or administered MST monotherapy or MST/AD combination treatment. At 8-week evaluation, patients were allowed to shift to MST monotherapy or adjust MST dose. Prophylactic laxatives were provided to MST patients. Final evaluation was performed at 12 weeks.

Adding Antidepressants, Benzodiazepines, and Zolpidem

One retrospective cohort study (Turner and Liang 2015[2]) examined 206,869 HMO patients (57% women) with chronic non-cancer pain (mean age 44 years) who had filled at least two Schedule II or III prescriptions for non-injectable opioid analgesics from January 2009 through July 2012. The study used

repeated measures logistic regression to evaluate interactions of filled prescriptions (including opioids, benzodiazepines, antidepressants, and zolpidem) with mental health disorders (anxiety/PTSD, depression, and psychotic disorder) in regard to drug overdose. Other factors included in the analyses were age, gender, region, SUD, clinical conditions, and opioid dose. Drug overdose recorded after the first filled prescription was the primary outcome. Follow up was 3.5 years.

Adding Pregabalin

The Baron et al. 2015[3] double-blind RCT (313 patients) evaluated the tolerability of tapentadol PR (300 mg/day) and pregabalin (300 mg/day) combination therapy versus a higher dose of tapentadol PR (500 mg/day) alone for treating severe CLBP with a neuropathic component. Duration of pain was over 8.5 years for both arms (9.4±10.48 tapentadol PR, 8.7±9.28 tapentadol PR/pregabalin). Mean age was over 55 years (58.5±11.01 tapentadol PR, 56.3±11.83 tapentadol PR/pregabalin) with more women enrolled than men (61.7% tapentadol PR, 54.1% tapentadol PR/pregabalin). AE-related outcomes included incidence of serious TEAEs and a composite outcome (dizziness and/or somnolence).

Adding SSRIs/SNRIs

Peniston et al. 2012[1] was a post-hoc pooled analysis of 2 RCTs (NCT00225797 and NCT00226421) that evaluated the concomitant use of SSRIs/SNRIs with oxymorphone ER in 348 patients with moderate-to-severe CLBP (47 oxymorphone ER/placebo plus SSRIs/SNRIs, 301 oxymorphone ER/placebo). The open-label phase (575 patients) was a titration phase followed by a withdrawal double-blind treatment phase (348 patients). Patients were randomly allocated to receive a stabilized dose of oxymorphone ER or placebo every 12 hours for 12 weeks. The mean age of the patients was around 48 years; only 27% of males were taking SSRIs/SNRIs (27.7% oxymorphone ER plus SSRIs/SNRIs, 53.5% oxymorphone ER). Most patients taking SSRIs/SNRIs (75%) reported a history of depression. No information was provided on exclusionary criteria or quality of the included studies.

Outcomes and Synthesis of Results

Below we provide reports of adverse events. Additional information and results are provided in Table 2.

Adding Antidepressants

One large retrospective cohort[2] assessed the risk of overdose of opioids (unspecified) plus ADs. One prospective comparison study reported tolerability of MST/ADs.[4]

Overdose: For patients with depression, long-term AD usage (91–180 days) was protective, with 20% lower AORs for overdose versus short-term (1–30 days) or none. For persons without depression, the AORs of overdose were increased for AD use, but greatest (AOR 1.98, 95% CI: 1.48 to 2.65) for short-term use versus none.

Adverse events: At 8 weeks, slightly fewer MST/AD patients reported tolerable side effects and maintained therapy (29.6% MST, 27.5% MST/AD). Combination therapy lessened the total frequency of side effects of both MST and AD (MST: 12.4% combination therapy, 21.2% MST monotherapy; AD: 18.6% combination therapy, 37.6% AD monotherapy).[4]

Adding Benzodiazepines

One large retrospective cohort[2] assessed the risk of overdose of opioids (unspecified) plus benzodiazepines.

Overdose: For all patients, the AORs of overdose increased with duration of benzodiazepine with >2.5-fold higher AORs for 91–180 days (with or without PTSD/anxiety) vs none.

Adding Pregabalin

One RCT evaluated the tolerability of pregabalin with tapentadol PR.[3]

TEAEs: Percent of patients reporting ≥1 TEAE were similar between groups (63.6% tapentadol PR, 64.8% tapentadol PR/pregabalin).

Serious TEAEs: Incidence of serious TEAEs was lower in the tapentadol PR/pregabalin group (1.9% tapentadol PR/pregabalin, 3.2% tapentadol PR group).

Composite AEs: Post-hoc analysis indicated significantly lower incidence of the composite of dizziness and/or somnolence with tapentadol PR versus tapentadol PR/pregabalin (16.9% tapentadol PR, 27.0% tapentadol PR/pregabalin; p=0.0302).

Dizziness: Higher with pregabalin (11% tapentadol PR, 17.6% tapentadol PR/pregabalin).

Somnolence: Higher with pregabalin (8.4% tapentadol PR, 11.9% tapentadol PR/pregabalin).

Fatigue: Higher with pregabalin (8.4% tapentadol PR, 10.1% tapentadol PR/pregabalin).

Headache: Higher with pregabalin (6.5% tapentadol PR, 8.2% tapentadol PR/pregabalin).

Dry mouth: Higher with pregabalin (3.9% tapentadol PR, 5.0% tapentadol PR/pregabalin).

Constipation: Lower with pregabalin (7.1% tapentadol PR, 5.0% tapentadol PR/pregabalin).

Vomiting: Lower with pregabalin (5.8% tapentadol PR, 3.1% tapentadol PR/pregabalin) Hyperhidrosis: Lower with pregabalin (11.7% tapentadol PR, 6.3% tapentadol PR/pregabalin).

Nausea: Lower with pregabalin (10.4% tapentadol PR, 9.4% tapentadol PR/pregabalin).

Diarrhea: Lower with pregabalin (3.9% tapentadol PR, 1.9% tapentadol PR/pregabalin).

Adding SSRIs/SNRIs

One post-hoc analysis of 2 RCTs (Peniston et al. 2012[1]) assessed the tolerability of adding SSRIs/SNRIs to oxymorphone ER.

Incidence of adverse events (AEs): No significant differences were reported between oxymorphone ER plus SSRIs/SNRIs and oxymorphone ER.[1]

Serious AEs (double-blind): No significant between-group difference was reported (3.4% oxymorphone ER plus SSRIs/SNRIs, 2.0 oxymorphone ER; p=0.65).[1]

Serious AEs (open label): Significantly more serious AEs occurred in oxymorphone ER plus SSRIs/SNRIs (3.4% oxymorphone ER plus SSRIs/SNRIs, 0.8% oxymorphone ER; p=0.04).[1]

Adding Zolpidem

One large retrospective cohort[2] assessed the risk of overdose of opioids (unspecified) plus zolpidem.

Zolpidem usage: For patients with anxiety/PTSD, the AORs of overdose were greatest for 31–90 days vs. none (AOR 1.77, 95% CI: 1.25 to 2.51). For patients without anxiety/PTSD, the AORs of overdose were greatest for short-term use versus none (AOR 1.67 (95 % CI: 1.21 to 2.30).

Overall Quality of Evidence Rating

Table 1 presents the overall quality ratings for the outcomes reported in the studies included as evidence for this key question. The overall quality of the evidence was assessed for each outcome using the GRADE system, which assigns a rating of High, Moderate, Low or Very low.

One non-RCT (Mustafa et al. 2010[4]) reporting on the tolerability of MST/AD combination therapy found very low quality evidence for adverse events. This rating was due to limitations in the methodological quality of the study (lack of randomization or attention to confounders) as well as imprecision (reporting by one study with no measures of dispersion). One retrospective cohort study (Turner and Liang 2015[2]) addressing the interaction of filled prescriptions (opioids, antidepressants, benzodiazepines, zolpidem) with mental health disorders found low quality evidence for overdose. This rating was due to limitations in the methodological quality of the study. One RCT evaluating the addition of pregabalin to tapentadol PR found moderate quality of evidence for all AE-related outcomes. The moderate quality rating was due to lack of reporting measures of dispersion.[3] One post-hoc analysis addressing use of oxymorphone ER with/without SSRIs/SNRIs found very low quality of evidence for AE-related outcomes due to very serious study limitations (lack of information on study quality of primary studies, high attrition) and serious imprecision (lacking measures of dispersion).[1]

Table 1. Overall Assessment of Quality of Evidence Base

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Adding Antidepressants								
Overdose	1 retrospective cohort study (Turner and Liang 2015[2])	Adding antidepressants (ADs) to unspecified opioids (206,869 patients)	For patients with depression, long-term AD usage (91–180 days) was protective, with 20% lower adjusted odds ratios (AORs) for overdose versus short-term (1–30 days) or none. For persons without depression, the AORs of overdose were increased for AD use, but greatest (AOR 1.98, 95% CI: 1.48 to 2.65) for short-term use versus none.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Adverse events	1 prospective comparison (Mustafa et al. 2010[4])	Morphine sulfate tablet (MST) vs. MST plus AD (MST/AD) (527 patients)	At 8 weeks, slightly fewer MST monotherapy patients reported tolerable side effects and maintained therapy (29.6% MST, 27.5% MST/AD). Combination therapy lessened the frequency of side effects of both MST and AD MST: 12.4% combination therapy 21.2% MST monotherapy; AD: 18.6% combination therapy, 37.6% AD monotherapy).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Single study, no measures of dispersion)	Very low
Adding Benzodiazepines								
Overdose	1 Retrospective cohort study (Turner and Liang 2015[2])	Adding benzodiazepines to unspecified opioids (206,869 patients)	For all patients, the AORs of overdose increased with duration of benzodiazepine with >2.5-fold higher AORs for 91–180 days (with or without PTSD/anxiety) vs. none.	Serious limitations(-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Adding Pregabalin								
TEAEs (double-blind)	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Percent of patients reporting ≥1 TEAE were similar between groups (63.6% tapentadol PR, 64.8% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Composite AEs	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Post-hoc analysis indicated significantly lower incidence of the composite of dizziness and/or somnolence with tapentadol PR versus tapentadol PR/pregabalin (16.9% tapentadol PR, 27.0% tapentadol PR/pregabalin; p=0.0302).	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Serious TEAEs	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Incidence was lower with pregabalin (1.9% tapentadol PR/pregabalin, 3.2% tapentadol PR group).	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Dizziness	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Higher with pregabalin (11% tapentadol PR, 17.6% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Somnolence	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Higher with pregabalin (8.4% tapentadol PR, 11.9% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Fatigue	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/pregabalin (300 mg/day) (313 patients)	Higher with pregabalin (8.4% tapentadol PR, 10.1% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Headache	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Higher with pregabalin (6.5% tapentadol PR, 8.2% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Dry mouth	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Higher with pregabalin (3.9% tapentadol PR, 5.0% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Constipation	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Lower with pregabalin (7.1% tapentadol PR, 5.0% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Hyperhidrosis	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Lower with pregabalin (11.7% tapentadol PR, 6.3% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Nausea	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Lower with pregabalin (10.4% tapentadol PR, 9.4% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Vomiting	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Lower with pregabalin (5.8% tapentadol PR, 3.1% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate
Diarrhea	1 RCT (Baron et al. 2015[3])	Tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/ pregabalin (300 mg/day) (313 patients)	Lower with pregabalin (3.9% tapentadol PR, 1.9% tapentadol PR/pregabalin)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Adding SSRIs/SNRIs								
Incidence of adverse events (AEs)	Post-hoc analysis of 2 RCTs (Peniston et al. 2012[1])	Oxymorphone ER plus SSRIs/SNRIs vs. oxymorphone ER (348 patients)	No significant differences were reported between oxymorphone ER plus SSRIs/SNRIs and oxymorphone ER groups.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Very low
Serious AEs (double-blind)	Post-hoc analysis of 2 RCTs (Peniston et al. 2012[1])	Oxymorphone ER plus SSRIs/SNRIs vs. oxymorphone ER (348 patients)	No significant between-group difference was reported (3.4% oxymorphone ER plus SSRIs/SNRIs, 2.0 oxymorphone ER; p=0.65).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Very low
Serious AEs (open label)	Post-hoc analysis of 2 RCTs (Peniston et al. 2012[1])	Oxymorphone ER plus SSRIs/SNRIs vs. oxymorphone ER (348 patients)	Significantly more serious AEs occurred in oxymorphone ER plus SSRIs/SNRIs group (3.4% oxymorphone ER plus SSRIs/SNRIs, 0.8% oxymorphone ER; p=0.04).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (No measures of dispersion)	Very low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Adding Zolpidem								
Overdose	1 retrospective cohort study (Turner and Liang 2015[2])	Adding zolpidem to unspecified opioids (206,869 patients)	For patients with anxiety/PTSD, the AORs of overdose were greatest for 31–90 days vs. none (AOR 1.77, 95% CI: 1.25 to 2.51). For patients without anxiety/PTSD, the AORs of overdose were greatest for short-term use versus none (AOR 1.67 (95 % CI: 1.21 to 2.30).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

[a] Methodological Quality takes into account the overall risk of bias rating of all the studies included in the evidence base;
[b] Inconsistency of results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed);
[c] Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population; and
[d] Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.

AD: antidepressant; AOR: adjusted odds ratio; CI: confidence interval; ER: extended release; MST: morphine sulfate tablet; PR: prolonged release; PTSD: posttraumatic stress disorder; RCT: randomized controlled trial; SNRI: serotonin–norepinephrine reuptake inhibitors; SSRI: selective serotonin re-uptake inhibitors; TEAE: treatment emergent adverse event

Appendix A. Evidence Tables

Table 2. Individual Studies

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Adding Antidepressants			
Reference: Mustafa et al. 2010[4] **Country:** Egypt **Study Design:** Prospective comparative study **Purpose:** To evaluate analgesic efficacy of oral morphine sulphate tablet (MST) monotherapy versus combination MST with antidepressants (ADs) for chronic pain management **Quality Rating:** Poor Non-randomized, limited baseline characteristics reported, no attention to confounders	**Number of Patients:** 527 (119 AD, 210 MST/AD, 198 MST) **Diagnosis:** Chronic pain (360 with cancer pain and 167 with non-cancer pain) **Age (Years):** Mean 46.5±6.7 **Gender:** Male 64.9% **Inclusion Criteria:** Patients attending Pain Clinic at Kasr Al-Eni Hospital for treatment of chronic pain, irrespective of its etiology were included. **Exclusion Criteria:** Patients who were on other lines of analgesia or received other opioids than MST or received MST in combination with other drugs were not enrolled.	After 4-weeks of ADs, treatment was modified based on VAS pain scores and side effects. Patients who showed significantly lower VAS score with tolerable side effects continued on ADs. Remaining patients either shifted to MST monotherapy or MST/AD combination therapy. Patients were re-evaluated at 8 and 12 weeks. **Primary Outcome**: Pain severity (pain score) **Secondary Outcome**: Adverse events **Follow-up:** 12 weeks	**Adverse Events**: At 8 weeks, slightly more MST monotherapy patients reported tolerable side effects and maintained therapy (29.6% MST, 27.5% MST/AD). Combination therapy lessened the frequency of side effects of both MST and AD (MST: 12.4% combination therapy, 21.2% MST monotherapy; AD: 18.6% combination therapy, 37.6% AD monotherapy).
Adding Antidepressants, Benzodiazepines, and Zolpidem			
Reference: Turner and Liang 2015[2] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To examine interactions of filled prescriptions for opioids, benzodiazepines, antidepressants, and zolpidem with mental health disorders in regard to drug overdose **Quality Rating**: Fair	**Number of Patients:** 206,869 (1,385 any drug overdose event; 205,484 no drug overdose event) **Diagnosis:** Non-cancer pain **Age in Years (mean±SD):** 44±12 **Gender:** Women 57% **Inclusion Criteria:** Individuals aged 18 to 64 years with non-cancer pain who filled at least two Schedule II or III prescriptions for non-injectable opioid analgesics from January 2009 through July 2012. Eligible subjects were continuously enrolled at least 12 months in the Aetna plan and had claims for service utilization at least 6 months before the first drug overdose event.	**Drug Usage (1st 6-month Interval):** 100% non-injectable opioids, 69% antidepressants, 45% benzodiazepines, 20% zolpidem **Primary Outcome:** Drug overdose diagnosed from an inpatient or outpatient clinical encounter following the first filled opioid prescription, measured in each 6-month interval after the first filled opioid prescription until last enrollment or end of the study Using repeated-measures logistic regression with the generalized estimating equations method under an unstructured correlation matrix,	**Antidepressants:** For patients with depression, long-term AD usage (91–180 days) was protective, with 20% lower AORs for overdose versus short-term (1–30 days) or none. For persons without depression, the AORs of overdose were increased for antidepressant use, but greatest (AOR 1.98, 95% CI: 1.48 to 2.65) for short-term use versus none. **Benzodiazepine:** For all patients, the AORs of overdose increased with duration of benzodiazepine with >2.5-fold higher AORs for 91–180 days (with or without PTSD/anxiety) vs. none. **Zolpidem:** For patients with anxiety/PTSD, the AORs of overdose were greatest for 31-90 days vs. none (AOR 1.77, 95% CI: 1.25 to 2.51). For patients without anxiety/PTSD, the AORs of

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Good participation and low attrition, multivariate analysis controlled for most potential confounders. Limitations were use of coded diagnoses with limited sensitivity for mental health disorders; adherence to prescriptions could not be determined; some overdoses may have been due to illicit drug use.	**Exclusion Criteria:** Individuals were excluded for the following reasons: enrolled <12 months, missing demographic data, age <18 or >64 years, incomplete opioid prescription data, <2 Schedule II or III opioid analgesic prescriptions, missing diagnostic data, cancer diagnosis, opioid abuse/dependence diagnosis prescribed methadone or buprenorphine, incomplete prescriber data, and <6 months enrollment after the first opioid analgesic prescription.	the authors examined the effects of daily opioid dose and duration of filled prescriptions for psychoactive drugs on the odds of overdose, adjusting for time-fixed covariates (i.e., age, sex, and region) as well as time-varying covariates (i.e., chronic pain conditions, mental health, and substance use disorders). Clinical judgment guided a backward model selection procedure. The authors started with a full model including demographics, clinical conditions, substance use disorders (i.e., drug or alcohol), and medications, as well as all possible interactions of daily opioid dose with each of the three psychoactive drug groups (i.e., benzodiazepines, antidepressants, and zolpidem), and interactions of each of these drugs with mental health conditions (i.e., anxiety/PTSD, depression, and psychotic disorder). The final model included clinically important and/or statistically significant factors. **Follow-up:** 3.5 years	overdose were greatest for short-term use vs. none (AOR 1.67 (95 % CI: 1.21 to 2.30).
Adding Pregabalin			
Reference: Baron et al. 2015[3] **Country:** Germany **Study Design:** RCT **Purpose:** To evaluate the effectiveness and tolerability of tapentadol PR monotherapy versus tapentadol PR/pregabalin combination therapy for severe chronic low back pain (CLBP) with a neuropathic component	**Number of Patients (Double-blind):** 313 (154 tapentadol PR; 159 tapentadol PR/pregabalin) **Diagnosis:** CLBP ≥3 months **Duration of Pain, Years (Mean±SD**): 9.4±10.48 tapentadol PR, 8.7±9.28 tapentadol PR/pregabalin **Age in Years (Mean±SD):** 58.5±11.01 tapentadol PR, 56.3±11.83 tapentadol PR/pregabalin **Gender:** Tapentadol PR (61.7% female, 38.3% male), tapentadol PR/pregabalin (54.1% female, 45.9% male)	**Opioid Treatment (3-week Open Label):** Titration to tapentadol PR 300 mg/day **Opioid Treatment (Double-blind):** Tapentadol PR 500 mg/day or tapentadol PR 300 mg/day plus pregabalin 300 mg/day **Primary Outcome:** Change in average pain intensity (NRS-3) **Secondary Outcomes**: PGIC, CGIC, EQ-5D, SF-12 Health Survey and HADS scale. **Follow-up:** 10 weeks	**Treatment-emergent Adverse Events (TEAE) (Double-blind)**: Percent of patients reporting ≥1 TEAE were similar between groups (63.6% tapentadol PR, 64.8% tapentadol PR/pregabalin) **Composite AEs:** Post-hoc analysis indicated significantly lower incidence of the composite of dizziness and/or somnolence with tapentadol PR versus tapentadol PR/pregabalin (16.9% tapentadol PR, 27.0% tapentadol PR/pregabalin; p=0.0302). **TEAE (Double-blind)** **Dizziness:** 11% tapentadol PR, 17.6% tapentadol PR/pregabalin

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
Quality Rating: Good Double-blind. Good matching of baseline characteristics and greater than 80% follow-up. Efficacy data analyzed using LOCF approach. Allocation concealment methods not described.	**Inclusion Criteria:** Individuals aged ≥18 years with a diagnosis of CLBP lasting ≥3 months and requiring a strong (WHO step III) analgesic. Patients under regular, daily pretreatment with a WHO step I analgesic or no regular analgesic pretreatment were required to have an average pain intensity score ≥6 at the baseline visit on an 11-point numerical rating scale-3 (NRS-3). If patients were taking regular WHO step II or III analgesics or centrally acting co-analgesics on a daily basis for ≥2 weeks prior to enrollment, they must have had an increase of ≥1 point in pain intensity (NRS-3) at the baseline visit (after washout) compared with the enrollment visit. Patients were required to have a score on the painDETECT questionnaire, which was used to evaluate the likelihood of a neuropathic pain component to LBP (possible score of 0 to 38), of "positive" (score of 19 to 38) or "unclear" (score of 13 to 18) at the baseline visit. **Exclusion Criteria:** Women who were pregnant or breast-feeding; patients with LBP caused by cancer and/or metastatic diseases; any painful procedures (e.g., major surgery) planned during the study that could affect effectiveness and safety outcomes; concomitant autoimmune inflammatory conditions; severe cardiac impairment; moderate renal impairment; a history of or current moderate or severe hepatic impairment; and other clinically significant diseases, laboratory findings, or active systemic or local infections that may affect efficacy or safety assessments were excluded. Patients were also excluded from the study if they had a history of any of the following: alcohol or drug abuse; seizure disorder or epilepsy; mild or moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within 1 year of enrollment; or severe traumatic brain injury within 15 years of enrollment or residual sequelae, suggesting transient changes in consciousness. In addition, patients		**Somnolence:** 8.4% tapentadol PR, 11.9% tapentadol PR/pregabalin **Hyperhidrosis:** 11.7% tapentadol PR, 6.3% tapentadol PR/pregabalin **Nausea:** 10.4% tapentadol PR, 9.4% tapentadol PR/pregabalin **Fatigue:** 8.4% tapentadol PR, 10.1% tapentadol PR/pregabalin **Headache:** 6.5% tapentadol PR, 8.2% tapentadol PR/pregabalin **Constipation:** 7.1% tapentadol PR, 5.0% tapentadol PR/pregabalin **Vomiting:** 5.8% tapentadol PR, 3.1% tapentadol PR/pregabalin **Dry mouth:** 3.9% tapentadol PR, 5.0% tapentadol PR/pregabalin **Diarrhea:** 3.9% tapentadol PR, 1.9% tapentadol PR/pregabalin **Serious TEAEs:** Incidence of serious TEAEs was lower in the tapentadol PR/pregabalin group (1.9% tapentadol PR/pregabalin, 3.2% tapentadol PR). **Serious TEAEs (Tapentadol PR):** 1 each chest injury, fall, tachycardia, vertigo, upper abdominal pain, and flank pain **Serious TEAEs (Tapentadol PR/pregabalin):** 1 each nausea, goiter, chest pain, hyperhidrosis, and thrombosis **Discontinued due to TEAEs:** Rates were similar between groups (7.8% tapentadol PR, 7.5% tapentadol PR/pregabalin **Stopped Treatment due to TEAEs (Continued in Open Label Pickup Arm):** Rates were slightly higher in tapentadol PR group (12.3% tapentadol PR, 11.3% tapentadol PR/pregabalin)

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
	with a history of allergy or hypersensitivity to tapentadol, pregabalin, paracetamol, or their excipients were excluded, as were those who had contraindications and warnings related to tapentadol, pregabalin, or paracetamol that were not covered by other exclusion criteria, including acute or severe bronchial asthma, severe respiratory depression with hypoxia and/or hypercapnia, cor pulmonale, severe chronic obstructive pulmonary disease, or non-opioid induced paralytic ileus.		
Adding SSRIs/SNRIs			
Reference: Peniston et al. 2012[1] **Country:** USA **Study Design:** Post-hoc pooled analysis of 2 RCTs **Purpose:** To assess the tolerability of oxymorphone ER for CLBP in patients taking selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) compared with patients not taking SSRIs/SNRIs. **Quality Rating**: Poor No risk of bias assessment or consideration of individual study quality, close to 50% attrition	**Number of Patients (Double-blind):** 348 (47 oxymorphone ER plus SSRIs/SNRIs, 301 oxymorphone ER) **Number of patients (Open Label):** 575 (89 oxymorphone ER plus SSRIs/SNRIs, 486 oxymorphone ER) **Diagnosis:** CLBP **Age in Years (Mean±SD):** 48.1±8.9 oxymorphone ER plus SSRIs/SNRIs, 48.7±13.1 oxymorphone ER **Gender (% Male):** 27.7% oxymorphone ER plus SSRIs/SNRIs, 53.5% oxymorphone ER **Inclusion Criteria:** Opioid-naïve and opioid-experienced individuals aged ≥18 years with moderate-to-severe CLBP that was symptomatic for at least several hours per day for ≥3 months. Opioid-naïve patients had to be taking less than the equivalent of oxycodone 5 mg/day during the 14 days before screening. Opioid-experienced patients had to be on around-the-clock oral opioid pain medication (morphine 60–660 mg/day or equivalent) for 2 weeks before screening. **Exclusion Criteria:** Not reported	**Oxymorphone ER Dose (End of Titration Phase):** Patients using SSRIs/SNRIs: 78.7±61.0 mg/day Patients not using SSRIs/SNRIs: 56.2±46.4 mg/day **Primary Outcome**: Tolerability (TEAE) **Secondary Outcome**: Efficacy (VAS) **Follow-up:** 12 weeks	**Incidence of Adverse Events (AEs):** No significant differences were reported between oxymorphone ER plus SSRIs/SNRIs and oxymorphone ER. Experienced ≥1 AE (open label): 75.3% oxymorphone ER plus SSRIs/SNRIs, 68.1% oxymorphone ER; p=0.18 Experienced ≥1 TEAE (open label): 59.6% oxymorphone ER plus SSRIs/SNRIs, 58.3% oxymorphone ER; p=0.82 Experienced ≥1 AE (double-blind): 62.1% oxymorphone ER plus SSRIs/SNRIs, 50.7% oxymorphone ER; p=0.26 Experienced ≥1 TEAE (double-blind): 34.5% oxymorphone ER plus SSRIs/SNRIs, 24.7% oxymorphone ER; p=0.27 **Serious AEs (Open Label):** Significantly more serious AEs occurred in oxymorphone ER plus SSRIs/SNRIs group (3.4% oxymorphone ER plus SSRIs/SNRIs, 0.8% oxymorphone ER; p=0.04). **Serious AEs (Double-blind):** No significant between-group difference was reported (3.4% oxymorphone ER plus SSRIs/SNRIs, 2.0 oxymorphone ER; p=0.65). **Frequently Reported AEs (Open Label)** **Constipation:** 20.2% oxymorphone ER plus SSRIs/SNRIs, 19.8% oxymorphone ER; p=0.92

Study Details	Patients/Interventions	Intervention/Treatment	Outcomes/Results
			Dizziness: 5.6% oxymorphone ER plus SSRIs/SNRIs, 8.4% oxymorphone ER; p=0.37 **Flushing:** 3.4% oxymorphone ER plus SSRIs/SNRIs, 0.8% oxymorphone ER; p=0.04 (significant difference not noted by authors) **Headache:** 11.2% oxymorphone ER plus SSRIs/SNRIs, 6.2% oxymorphone ER; p=0.08 **Nausea:** 18.0% oxymorphone ER plus SSRIs/SNRIs, 17.9% oxymorphone ER; p=0.99 **Pruritus: 7.9%** oxymorphone ER plus SSRIs/SNRIs, 6.6% oxymorphone ER; p=0.66 **Somnolence:** 10.1% oxymorphone ER plus SSRIs/SNRIs, 16.3% oxymorphone ER; p=0.14 **Vomiting:** 6.7% oxymorphone ER plus SSRIs/SNRIs, 5.8% oxymorphone ER; p=0.72 **Frequently reported AEs (Double-blind)** **Constipation:** 10.3% oxymorphone ER plus SSRIs/SNRIs, 4.8% oxymorphone ER; p=0.24 **Dizziness:** 6.9% oxymorphone ER plus SSRIs/SNRIs, 2.0% oxymorphone ER; p=0.15 **Flushing:** 3.4% oxymorphone ER plus SSRIs/SNRIs, 1.4% oxymorphone ER; p=0.43 **Headache:** 0% oxymorphone ER plus SSRIs/SNRIs, 1.4% oxymorphone ER; p=0.53 **Nausea:** 6.9% oxymorphone ER plus SSRIs/SNRIs, 6.2% oxymorphone ER; p=0.88 **Pruritus:** 3.4% oxymorphone ER plus SSRIs/SNRIs, 1.4% oxymorphone ER; p=0.43 **Somnolence:** 3.4% **o**xymorphone ER plus SSRIs/SNRIs, 1.4% oxymorphone ER; p=0.43 **Vomiting:** 0% oxymorphone ER plus SSRIs/SNRIs; 2.0% oxymorphone ER; p=0.44 **Discontinued due to AEs (Excluding Placebo Patients):** 6.9% oxymorphone ER plus SSRIs/SNRIs; 9.6% oxymorphone ER

AD: antidepressant; AE: adverse event; AOR: adjusted odds ratio; CI: confidence Interval; CGIC: clinician global impression of change; CLBP: chronic low back pain; ER: extended release; EQ-5D: EuroQol-5 Dimension health status index; HADS: hospital qnxiety and depression scale; LOCF: last observation carried forward; MST: morphine sulfate tablet; NPSI: neuropathic pain symptom inventory; PR: prolonged release; PGIC: patient global impression of change; RCT: randomized controlled trial; SD: standard deviation; SNRI: serotonin–norepinephrine reuptake inhibitors; SSRI: selective serotonin re-uptake inhibitors; SF-12: Short Form-12 health survey; TEAE: treatment emergent adverse events; VAS: visual analog pain scale

Appendix B. References

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Appendix C. Excluded Studies

Table 3. Excluded Studies

Reference	Reason for Exclusion
Park T et al. 2015[5]	Does not meet study design criteria; unknown percentage of population for acute and chronic pain.
Banerjee M et al. 2014[6]	Population not of interest (e.g., under 18 years)
Skurtveit S et al. 2014[7]	Not a systematic review or clinical trial of any design

Key Question 7: What is the comparative effectiveness of different risk mitigation strategies for patients either on COT or being considered for COT? a.) Does this differ for patients with history of or current SUD? b.) Does this differ for patients with mental health comorbidities? c.) Does this differ for patients with medical comorbidities?